Clinical Trial Protocol

A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Investigational product:	**CBP-201**
Protocol number:	**CBP-201-CN002**
Version number:	**4.0**
Date:	**August 1, 2022**
Sponsor:	**Suzhou Connect Biopharmaceuticals, Ltd.**
NCT Number:	**NCT05017480**

Protocol Signature Page—Principal Investigator

Study title: A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Protocol number: CBP-201-CN002

The signature below indicates that the principal investigator has read and understood the clinical study protocol and its amendments, and agrees to conduct this study in accordance with the content of the study protocol, the *Declaration of Helsinki*, the *Good Clinical Practice for Pharmaceuticals*, and all applicable regulatory requirements. I will provide all the study staff participating in this study with a copy of this protocol and discuss the protocol and related files with them to ensure that they fully understand the study drug and how to conduct this study.

Signature

Name of principal investigator:	**Zhang Jianzhong** 主要研究者姓名：张建中
Signature:	签名： 日期：2022.8.3 **Date:**
Name of study facility:	**Peking University People's Hospital**
Address of study facility:	**No. 11, Xizhimen South Street, Xicheng District, Beijing**

Protocol Signature Page—Sponsor

Protocol title: A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Protocol number: CBP-201-CN002

The signature below indicates that the sponsor has read and understood the clinical study protocol and its amendments, and agrees to conduct this study in accordance with the content of the study protocol, the *Declaration of Helsinki*, the *Good Clinical Practice for Pharmaceuticals*, and all applicable regulatory requirements.

Signature

Name of the sponsor's person in charge:	Guo Jiawang
	Clinical Operation Director
Signature:	申办者负责人姓名：郭家旺 临床运营总监 签名：郭家旺 **Date:** 日期：2022.8.2
Name of the sponsor	**Suzhou Connect Biopharmaceuticals, Ltd.**

Protocol Signature Page—Statistical Analysis Unit

Study title: A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Protocol number: CBP-201-CN002

The signature below indicates that the statistical analysis unit has read and understood the clinical study protocol and its amendments, and agrees to conduct this study in accordance with the content of the study protocol, the *Declaration of Helsinki*, the *Good Clinical Practice for Pharmaceuticals*, and all applicable regulatory requirements.

Signature

Name of the statistical analysis unit's person in charge: Xu Jinmei

统计分析单位负责人姓名：徐进梅

签名：徐进梅 日期：2022年8月5日

Signature: **Date:**

Name of statistical unit: **Hangzhou Tigermed Consulting Co., Ltd.**

Protocol Signature Page—Statistical Analysis Unit (Pharmacokinetics)

Study title: A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Protocol number: CBP-201-CN002

The signature below indicates that the statistical analysis unit has read and understood the clinical study protocol and its amendments, and agrees to conduct this study in accordance with the content of the study protocol, the *Declaration of Helsinki*, the *Good Clinical Practice for Pharmaceuticals*, and all applicable regulatory requirements.

Signature

Name of the statistical analysis unit's person in charge:	Sun Xiaoyan 统计分析单位负责人姓名：孙晓燕
Signature:	签名：  **Date:** 日期：2022/08/04
Name of statistical unit:	**Hangzhou Tigermed Consulting Co., Ltd.**

Protocol Signature Page—Other Study Centers

Study title: A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis

Protocol number: CBP-201-CN002

The signature below indicates that the investigator has read and understood the clinical study protocol and its amendments, and agrees to conduct this study in accordance with the content of the study protocol, the *Declaration of Helsinki*, the *Good Clinical Practice for Pharmaceuticals*, and all applicable regulatory requirements.

Signature

Name of investigator:	_____		
Signature:	_____	**Date:**	_____
Name of study facility:	_____		

Sponsor

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Project leader	Zhou Xuanyi			
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1. Protocol Synopsis

<table>
<tr><td>Sponsor</td><td>Suzhou Connect Biopharmaceuticals, Ltd.</td></tr>
<tr><td>Protocol number</td><td>CBP-201-CN002</td></tr>
<tr><td>Study title</td><td>A double-blind, multi-center, randomized controlled clinical study to evaluate the efficacy and safety of CBP-201 in Chinese subjects with moderate to severe atopic dermatitis</td></tr>
<tr><td>Version/date</td><td>V4.0/August 1, 2022</td></tr>
<tr><td>Phase</td><td>Phase II</td></tr>
<tr><td>Indication</td><td>Moderate to severe atopic dermatitis (AD)</td></tr>
<tr><td>Study objectives</td><td><u>Primary objective:</u>
To assess the efficacy of CBP-201 in subjects with moderate to severe AD
<u>Secondary objectives:</u>
To assess the safety and tolerability of CBP-201 in subjects with moderate to severe AD
To assess the pharmacokinetic (PK) characteristics of CBP-201 in subjects with moderate to severe AD
To assess the pharmacodynamic (PD) characteristics of CBP-201
To assess the immunogenicity of CBP-201</td></tr>
<tr><td>Study design</td><td>This study is a randomized, double-blind, multi-center, controlled study designed to assess the efficacy, safety and PK characteristics of CBP-201 in eligible subjects with moderate to severe AD.
The study includes a screening period, a treatment period and a follow-up period. The treatment period is divided into two stages:
<u>Stage 1 study:</u> It is a placebo-controlled study, in which subjects who meet the inclusion criteria and do not meet the exclusion criteria will be stratified according to the severity of their baseline disease (moderate [IGA=3] and severe [IGA=4]) and randomized into one of the following 2 groups to receive investigational product or placebo treatment by the ratio of 2:1:
Group A (CBP-201): the subjects will receive a subcutaneous injection of CBP-201 600 mg (4 ml in total, 2 injections of 2 ml each in different sites) on Day 1, begin to receive a subcutaneous injection of CBP-201 300 mg (2 ml) from Week 2 (W2), and receive treatment at the same dose every 2 weeks thereafter until W14;
Group B (placebo): the subjects will receive a subcutaneous injection of placebo 4 ml (2 injections of 2 ml each in different sites), begin to receive a subcutaneous injection of placebo 2 ml from W2, and receive placebo 2 ml every 2 weeks thereafter until W14.
The grouped dosing regimen in Stage 1 is shown in the table below:
<table>
<tr><th>Group</th><th>W0</th><th>W2</th><th>W4</th><th>W6</th><th>W8</th><th>W10</th><th>W12</th><th>W14</th></tr>
<tr><td>Group A</td><td>4XC</td><td>2XC</td><td>2XC</td><td>2XC</td><td>2XC</td><td>2XC</td><td>2XC</td><td>2XC</td></tr>
<tr><td>Group B</td><td>4XP</td><td>2XP</td><td>2XP</td><td>2XP</td><td>2XP</td><td>2XP</td><td>2XP</td><td>2XP</td></tr>
</table>
Note: C=CBP-201; P=placebo; #X=number of ampoules
Before the administration of study drug at W16 visit, all subjects will be assessed for efficacy, and the treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in</td></tr>
</table>

Eczema Area and Severity Index (EASI) score (ie EASI-50).

Stage 2 study: The grouping for Stage 2 maintenance treatment is as follows:

- Subjects who have achieved EASI-50 in the W16 pre-administration treatment assessment will be 1:1 randomized to one of the following two groups to receive study treatment starting from W16:
  - Group C: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 2 weeks until W50;
  - Group D: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 4 weeks. □ In order to maintain the injection every 2 weeks blind, when not receiving CBP-201, the subjects will receive an injection of placebo 2 ml once every 4 weeks until W50.
- Subjects who have not achieved EASI-50 in the W16 pre-administration treatment assessment will receive the following treatment starting from W16:
  - Group E: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 2 weeks until W50.
- If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.

The dosing regimen in Stage 2 is shown in the table below:

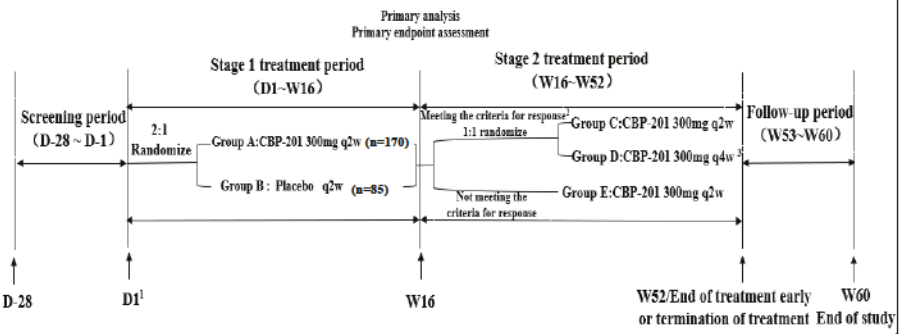
Group	W16	W18	W20	W22	W24	……	W50
Group C	2XC	2XC	2XC	2XC	2XC	……	2XC
Group D	2XC	2XP	2XC	2XP	2XC	……	2XP
Group E	2XC	2XC	2XC	2XC	2XC	……	2XC

Note: C=CBP-201; P=placebo; #X=number of ampoules

All subjects (including the subjects who are early terminated of the treatment) will be followed up for 8 weeks after the last dose.

In this study, an independent Data and Safety Monitoring Board (DSMB) will be established to regularly review and evaluate the cumulative study data, to guarantee the safety of subjects, implementation and progress of the study, and to give the sponsor a suggestion on whether to continue the study.

The overall study design is shown in the diagram below:



Note: 1. The subjects will receive a loading dose of the study drug (investigational product/placebo) on D1 at a dose of 600 mg (4 ml); 2. Response is defined as a 50% or more decrease in the EASI score; 3. In order to maintain

	the injection every 2 weeks blind, when not receiving CBP-201, the subjects will receive an injection of placebo 2 ml once every 4 weeks until W52; 4: If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.
Planned number of study sites	Approximately 55
Planned number of subjects to be enrolled	Expected to enroll about 255 cases (due to protocol changes, the actual number of subjects enrolled is expected to be approximately 336)
Study cycle	The study consists of a screening period, a treatment period (2 stages) and a follow-up period: • Screening period: D-28~D-1 • Treatment period: ○ Stage 1 treatment: 16 weeks (D1~W16) ○ Stage 2 maintenance treatment: 36 weeks (W16~W52) • Follow-up period: 8 weeks (W53~W60)
Study duration	The longest duration of each subject's participation in the study is 64 weeks (including a screening period of 4 weeks, Stage 1 treatment period of 16 weeks, Stage 2 maintenance treatment period of 36 weeks, and a follow-up period of 8 weeks). The study duration is expected to be about 2 years.
Eligibility criteria	**Inclusion criteria** Patients must meet all of the following criteria to be enrolled into this study: 1) 12≤ age ≤75 years at the screening visit, male or female; *note: the adolescent subjects aged <18 years should have body weight ≥40 kg.* 2) Diagnosed with atopic dermatitis (according to the American Academy of Dermatology's Guidelines of care for the management of atopic dermatitis, 2014[1]) at the screening, visit and: a) The subject has been suffering from the disease for more than 1 year at the time of screening, and according to the judgment of the investigator, the subject has had poor response to topical drugs such as corticosteroids, phosphodiesterase-4 (PDE-4) inhibitors or calcineurin inhibitors (TCI), or it is not medically suitable for the subject to receive topical drug treatment (e.g., there are important side effects or safety risks); Note: Poor response is defined as any of the following conditions: i. The patient has not achieved and maintained response or reached a low disease activity state (equivalent to IGA 0=asymptomatic to 2=mild) despite regular use of topical therapy during the 1 year before baseline; ii. The patient has received systemic treatment for AD despite regular use of topical therapy during the 1 year before baseline. b) At the screening and baseline visit, Investigator's Global Assessment (IGA) score ≥3 (according to the validated Investigator Global Assessment for Atopic Dermatitis [vIGA-AD™] scale, see Section 17.4 Appendix D), Eczema Area and Severity Index (EASI) score≥16 (see Section 17.5, Appendix E), and≥10% body surface area (BSA) of

	AD involvement(see Section 17.6, Appendix F); c) The average score of the maximum pruritus intensity in the Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 (see Section 17.1, Appendix A). Note: The baseline average maximum pruritus PP-NRS intensity score will be calculated based on the average value of the maximum pruritus intensity PP-NRS score [daily score range 0-10] every day within 7 days before randomization. In these 7 days, the scores of at least 4 days are required for the calculation of the baseline average score. If the patient's reporting days are less than 4 days in the 7 days before the planned date of randomization, randomization should be postponed until the requirements are met, but it is not allowed to exceed the maximum screening period of 28 days. 3) Able and willing to use a stable dose of a mild emollient at the AD involvement area at least twice a day starting from at least 7 days before baseline and continue to use it during the study period (see Section 8.1.1.2 Emollients). 4) Female subjects of childbearing potential (FCBP) and male subjects who have not undergone vasectomy must take highly effective contraceptive measures during the entire study period, including the 8-week follow-up period after discontinuation of study drug. *Postmenopausal women (determined by testing follicle stimulating hormone [FSH]) and women with a record of surgical sterilization (i.e., tubal ligation or hysterectomy or bilateral oophorectomy) before the screening visit can be considered infertile.* Highly effective contraceptive measures include: i. Abstinence (acceptable only if it is part of the subject's routine lifestyle); ii. Hormones (oral, patch, ring, injection, implant) combined with male condoms. This measure must be used at least 30 days before the first study drug administration. Otherwise, another acceptable method of contraception must be used; iii. Intrauterine device (IUD) combined with male condoms; iv. Exceptions are: a) women who have had amenorrhea for at least 12 consecutive months without using drugs known to cause amenorrhea, and have a recorded FSH level greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy). 5) Subjects and/or their guardians have the ability to learn the study requirements and process, and voluntarily take part in the clinical trial and sign an informed consent form (ICF); note: for subjects ≥18 years: subjects voluntarily agree to take part in the study by themselves and sign ICF; for subjects aged 12-17 years: subjects and their guardians voluntarily agree to take part in the study, the guardians sign the ICF, and the subjects sign the informed assent form for minors by themselves. 6) Subjects and/or their guardians are willing and able to comply with study visits and related procedures. **Exclusion criteria** Patients who meet any of the following criteria cannot participate in this study:

	1) Patients who have received any of the following treatments: a) Treatment with dupilumab or any anti-IL-4Rα or IL-13 antibodies; b) Topical drugs for treatment of AD or have the potential to affect the assessment of AD, including but not limited to corticosteroids, PDE-4 inhibitors, Janus kinase (JAK) inhibitors, aromatic hydrocarbon receptor agonists, tacrolimus or pimecrolimus, or traditional Chinese medicine (TCM) or herbal medicine, etc. within 2 weeks before baseline; c) Have undergone bleaching baths ≥ twice within 2 weeks before baseline; d) Have begun to use prescription emollients or emollients containing additives (e.g., ceramide, hyaluronic acid, urea, or filaggrin breakdown products) to treat AD from the screening period (if the subject has started using this kind of emollient before the screening visit, they can continue to use it at a stable dose; if the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period); e) Treatment with systemic corticosteroids or other immunosuppressive/immunomodulating substances (e.g., cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, or oral JAK inhibitors) due to AD or other diseases within 4 weeks before baseline (*except for corticosteroid inhalers and nasal sprays*); f) Treatment with systemic TCM or herbal treatment within 4 weeks before baseline (note: except for those for the treatment of diseases other than AD, which are necessary and will neither increase the risks of the subjects nor affect the assessment of the study in accordance with the medical judgements of the investigator and/or specialist physician); g) Treatment with phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), sunbed or any other light emitting device (LED) therapy within 4 weeks before baseline; h) Have used any investigational drug/treatment within 4 weeks before baseline or 5 drug half-lives, whichever is longer; i) Treatment with other biological agents (e.g., omalizumab) within 3 months before baseline or 5 drug half-lives (if known), whichever is longer; j) Have been vaccinated with live (attenuated) vaccine within 8 weeks before baseline; k) Treatment with cell depletion agents (e.g., rituximab) within 6 months before baseline; l) Treatment with allergen specific immunotherapy (SIT) within 6 months before baseline (except those who were already on stable-dose therapy before baseline). 2) Patients who meet any of the following: a) History of hypersensitivity to L-histidine, trehalose or Tween 80;

	b) Other skin complications in addition to AD that may interfere with the study assessments; c) Any history of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC); d) History of malignant tumor within 5 years before screening, except for cervical carcinoma in situ or non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma; e) Active tuberculosis (TB) at the screening visit, latent tuberculosis or a history of non-tuberculous Mycobacterium infection; Note: - Unless there is a clear specialist record proving that the patient has received adequate treatment and is currently able to start receiving biological treatment (based on the medical judgment of the investigator and/or infectious disease specialist); - If necessary, T-spot test may be used for auxiliary diagnosis of suspected tuberculosis patients; f) Positive for hepatitis B surface antigen (HBsAg), or positive for hepatitis B core antibody (HBcAb) and HBV-DNA, or positive for hepatitis C antibody and HCV RNA polymerase chain reaction; or serologically positive for human immunodeficiency virus (HIV) at the screening visit; g) Any of the following laboratory test abnormalities at the screening visit: i. Aspartate aminotransferase or alanine aminotransferase > 2 times the upper limit of normal (ULN), or total bilirubin > 1.5×ULN; ii. Serum creatinine > 1.2×ULN; iii. Hemoglobin < 8.5 g/dl (85.0 g/L) in male patients and < 8.0 g/dl (80.0 g/L) in female patients; iv. White blood cell count $<3.0\times10^9$/L or $\geq14\times10^9$/L; v. Platelet count $<100\times10^9$/L. Note: if the subjects have the above laboratory test abnormalities at screening, after being assessed as necessary by the investigator, they are allowed to receive a retest at another day within 28 days of the screening period, and those qualified for the retest are permitted to be enrolled (*it is forbidden to conduct drug intervention for those laboratory test abnormalities before retest*). h) Planning to undergo major surgical operations during the study period; i) Used systemic treatment with antibiotics, antiviral drugs, antiparasitic drugs, antigenic drugs, or antifungal drugs due to infection within 4 weeks before the baseline visit, or suffered from superficial skin infection (e.g., impetigo) within 2 weeks before baseline (after the infection subsides, the subjects can be rescreened); j) History of parasite infection (e.g., helminth) within 6 months before baseline; k) According to the investigator's judgment, there is a known or suspected history of immunosuppression within 6 months before baseline, including a history of invasive opportunistic infections, such as aspergillosis, coccidiosis, histoplasmosis, HIV, listeriosis, Pneumocystis or tuberculosis, even if the infection has subsided; or

<table>
<tr><td></td><td>there is an abnormally frequently recurrent or persistent infection;
l) History of alcohol or drug abuse within 2 years before the screening visit;
m) Any other medical or psychological condition (including clinically significant laboratory test abnormalities, electrocardiogram (ECG) parameters, etc.) at the screening visit, which, as judged by the investigator, may indicate new and/or insufficiently understood diseases, may put the patient at an unreasonable risk due to his/her participation in the clinical trial, may lead to unreliable results of the patient's participation, or may interfere with the study assessments. The specific reasons for patients excluded due to this criterion will be indicated in the study documents (medical records, electronic case report form [eCRF], etc.).
3) Pregnant or lactating women, or subjects with pregnancy or lactation plans during the study period.</td></tr>
<tr><td>Study drug</td><td>● Investigational drug/placebo
<table>
<tr><th>Study drug</th><th>Investigational drug</th><th>Placebo</th></tr>
<tr><td>Drug name</td><td>CBP-201</td><td>/</td></tr>
<tr><td>Dosage form</td><td colspan="2">Injection</td></tr>
<tr><td>Composition</td><td>CBP-201 is prepared from a solution containing inactive excipients (including NaCl, trehalose, Tween 80 and L-histidine) at a concentration of 150 mg/ml.</td><td>Contains the same excipients, but does not contain CBP-201 API.</td></tr>
<tr><td>Storage</td><td colspan="2">CBP-201 preparation and the corresponding placebo solution should be stored at 2-8 ℃.</td></tr>
<tr><td>Method of administration</td><td colspan="2">Subcutaneous injection (SC)</td></tr>
<tr><td>Dosing regimen</td><td colspan="2">Detailed in Section 6.1.</td></tr>
</table>
● Emollients
From at least 7 days before baseline to the end of the study, subjects will be required to apply a mild emollient to the AD involvement area at least twice a day as background treatment, but should avoid using emollients within 4 hours before AD assessment at each visit. If the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to the emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period.</td></tr>
<tr><td>Study cycle/steps</td><td>Screening period (D-28~D-1)
After the subjects and/or their guardians signing the ICF, the subjects will be assessed for study eligibility at the screening visit within 28 days prior to the baseline visit.
Baseline (D1)
Before D1 administration of study drug, subjects who were eligible at the screening visit will be confirmed again for their eligibility. After baseline assessment, the subjects who are confirmed to meet the inclusion criteria will</td></tr>
</table>

	be randomized to Group A (CBP-201) or Group B (placebo) in a 2:1 ratio. **Stage 1 treatment period (D1~W16)** Randomized subjects will receive CBP-201 or placebo SC administration (CBP-201 600 mg or placebo at D1, and CBP-201 300 mg or placebo, Q2W starting from W2). Vital signs monitoring will be conducted at the study site before D1, W2 and W4 administration and 2 hours after administration, and before and 30 minutes after each administration from W6 to W14. Before W16 administration, all subjects will be assessed for efficacy, and treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in EASI score (ie EASI-50). **Stage 2 treatment period (W16~W52)** Subjects who are assessed to have achieved EASI-50 before W16 administration will be 1:1 randomized to Group C or Group D and start receiving SC administration of CBP-201 300 mg Q2W or once every 4 weeks (Q4W) until W50 (If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.); subjects who are assessed to have not achieved EASI-50 before W16 administration will be assigned to Group E to start receiving SC injection of CBP-201 300 mg Q2W until W50. All subjects should undergo vital signs monitoring before administration and 2 h after administration at W16, W18 and W20 at the study site, and before and 30 min after each administration from W22 to W50. All subjects will return to the study site for examinations and assessments according to the time specified in the Study Flow Chart. Throughout the study period, AE assessment will be continued and concomitant medication/treatment information will be collected. **Follow-up period (W53~W60)** After the end of Stage 2 (W52), subjects will be followed up for safety and efficacy for 8 weeks to further explore the PK and PD characteristics of CBP-201, and return to the study site for examinations and assessments according to the time specified in the Study Flow Chart. If a subject early terminates (ET) the study for any reason, the subject should complete the ET visit within 7 days after ET, and complete the 8-week follow-up visit as much as possible after the ET visit. Blood samples from all subjects will be collected during the whole study period to evaluate the steady-state PK characteristics of CBP-201 and its PD effects on serum thymus activation regulated chemokine (TARC) level, total immunoglobulin E (IGE) level, peripheral blood eosinophil count and serum IL-4 and IL-13 levels, and to detect anti-drug antibodies (ADA) (*all ADA positive samples will be further tested for the presence of anti-CBP-201 neutralizing antibody [NAb]*). The detailed study procedures are shown in the Study Flow Chart.
Concomitant medications/treatments	**Prohibited drugs/treatments** The following drugs/treatments are prohibited during the study period. If any of the following treatment is started after the first dose of study drug on D1, the study treatment must be early terminated:

	• Dupilumab or any anti-il-4r α or IL-13 antibodies; • Topical PDE-4 inhibitors or JAK inhibitors; • Systemic treatment with corticosteroids or other immunosuppressive and/or immunomodulatory agents such as cyclosporine, mycophenolate mofetil, azathioprine, methotrexate or oral JAK inhibitors; • Cell depletion agents (e.g., rituximab) or other biological agents; • Other investigational drugs (non CBP-201) or treatments. The following treatments are also prohibited during the study period: • Initiation of SIT or dose up-regulation; • (Attenuated) live vaccine; • Topical corticosteroids (TCS) or TCI; • Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies; • Bleaching baths more than 2 times a week; • Any drug (except mild emollients) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity. **Permitted drugs/treatments** AD is a chronic recurrent skin disease characterized by periodic aggravation or gradual deterioration of symptoms. If medically necessary (i.e. in order to control intolerable AD symptoms), the investigator can provide patients with rescue therapy for AD by using drugs or treatment regimens that were originally prohibited at their own discretion. According to the investigator's judgment, AD aggravation or deterioration of symptoms which requires drugs or treatments originally prohibited by the protocol for rescue therapy will be defined as "AD recurrence" event, and the onset and duration of these events will be recorded as AE according to the site of attack. Note: The investigator should limit the first-step rescue therapy to topical drugs (TCS or TCI) as far as possible. Only patients who do not respond adequately after at least 7 days of topical medication can be upgraded to systemic medication or other treatments. If a subject receives systemic corticosteroid or non-steroid systemic immunosuppressive/immunomodulatory rescue therapy, the study drug administration will be stopped immediately. (refer to Section 8.2 for details) **Other drugs that are permitted may include:** • Emollients (as the background treatment of this study, at least 7 days before baseline, all subjects need to use mild emollients at least twice a day, and continue to use them throughout the study period. During the screening period or the study period, subjects cannot start using prescription emollients or emollients containing additives. However, if a subject has already started using these emollients before the screening visit, he/she needs to continue using them at a stable dose throughout the study period. If the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to the emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period.); • Basic skin care (cleansing and bathing);

	• Oral antihistamines (maintain a stable dose within 7 days before baseline and during the study period); • Drugs for the treatment of chronic diseases (e.g., hypertension, diabetes, etc.); • Local or systemic anti-infective drugs (as required by the condition). Before any rescue therapy, the investigator should make every effort to assess the efficacy and safety (e.g., disease severity score, safety laboratory tests). If necessary, unscheduled visits can be conducted.
Efficacy endpoints	**Primary endpoint:** The proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W16. **Key secondary endpoints:** • The proportion of subjects achieving EASI-75 at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 4 points from baseline at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 3 points from baseline at W16; • Change and percentage change in the weekly average PP-NRS from baseline at W16; • The proportion of subjects achieving EASI-90 at W16; **Other secondary endpoints:** • Change and percentage change in the EASI score from baseline at W16; • The proportion of subjects achieving EASI-50 at W16; • Percentage change in the BSA of AD involvement from baseline at W16; • Percentage change in the SCORAD score from baseline at W16; • Change in DLQI from baseline at W16; • Change in POEM from baseline at W16; • Percentage change in the weekly average PP-NRS from baseline at W2. **Other efficacy endpoints:** • The proportion of subjects whose IGA score is decreased by ≥ 2 points from baseline at W16; • The proportion of subjects achieving EASI-100 at W16; • The number of AD recurrences and number of days from baseline to W16; • Change in efficacy parameters (e.g., IGA, EASI, BSA, SCORAD, POEM and DLQI) from baseline to W16; • Change in weekly average PP-NRS from baseline at W16; • The proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W52; • The percentage decrease in the overall EASI score between W16 and W52; • The proportion of subjects achieving EASI-50 at W52; • The proportion of subjects achieving EASI-75 at W52;

	• The proportion of subjects achieving EASI-90 at W52; • The proportion of subjects achieving EASI-100 at W52; • Change in weekly average PP-NRS compared with baseline from W16 to W52; • Change in POEM compared with baseline from W16 to W52; • The proportion of subjects whose IGA score is decreased by ≥2 points from baseline at W52; • Percentage change in the AD-affected BSA compared with baseline from W16 to W52; • Change in SCORAD compared with baseline from W16 to W52; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥3 points from baseline at W52; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥4 points from baseline at W52; • Change in PDLQI compared with baseline from W16 to W52; • The number of subjects with AD recurrence from baseline to W8; • The number of subjects with AD recurrence from W8 to W16; • The number of subjects with AD recurrence from W16 to W52; • The number of AD recurrences and number of days from W16 to W52. Note: EASI 50: EASI score is decreased by ≥50% from baseline; EASI 75: EASI score is decreased by ≥75% from baseline; EASI 90: EASI score is decreased by ≥90% from baseline; EASI-100: EASI score is decreased by 100% from baseline; PP-NRS: Peak Pruritus Numerical Rating Scale; AD recurrence: According to the investigator's judgment, AD aggravation or deterioration of symptoms which requires drugs or treatments originally prohibited by the protocol for rescue therapy will be defined as "AD recurrence" event; POEM: Patient Oriented Eczema Measure; SCORAD: Scoring Atopic Dermatitis Index; DLQI: Dermatology Life Quality Index.
Safety endpoints	• Incidence and severity of AE, AE of special interest (AESI) and serious adverse event (SAE); • Abnormal changes in vital signs, physical examination, and the injection site; • Abnormal changes in laboratory tests, ECG parameters, etc.; • Percentage of subjects positive for ADA.
PK endpoints	To analyze the blood concentration of CBP-201, and calculate the PK characteristics of steady-state trough concentrations of individuals and each group of subjects at each treatment time point.
PD endpoints	Change in serum IL-4, IL-13, IgE, TARC levels and peripheral blood eosinophil count from baseline.
Statistical analysis methods	**Determination of sample size** The sample size of 255 cases (in a 2:1 ratio, 170 cases in the CBP-201 300 mg Q2W group, and 85 cases in the placebo group. Assume that the dropout rate in the treatment group is 15%, then about 144 cases in the CBP-201 300 mg Q2W group and 72 cases in the placebo group will be able to complete the study) can provide a power of 90% to detect the therapeutic effect on the primary endpoint in the CBP-201 300 mg Q2W group and the placebo group. This power is

	calculated based on the following assumption: the proportion of subjects reaching the primary efficacy endpoint is 27% in the CBP-201 300 mg Q2W group and 9% in the placebo group, and the significance level for two-sided tests is 0.05. The primary analysis of this study will still be based on the 255 subjects enrolled in accordance with V2.1 and its earlier versions of the protocol. Subjects newly enrolled (approximately 81 cases) based on the protocol after V2.1 will not be included in the primary analysis, and only supplementary analysis will be performed. **Statistical analysis populations** In this study, it is planned to perform statistical analyses in two stages: First of all, after the 255 subjects enrolled based on the V2.1 and prior versions of the protocol complete the administration and treatment, related evaluations and follow-up of Stage 1 (W16 pre-dose visit), the primary analysis will be performed based on the data of the 255 subjects, and the following 6 analysis populations are defined as: • Screening set 1 will include all subjects who have signed the ICF. • Randomization set 1 will include all subjects randomized at baseline (D1), regardless of whether they have received the treatment of study drug. • Full analysis set 1 (FAS1) will include all subjects in randomization set 1 who have received at least one dose of the study drug. FAS1 will determine the treatment groups based on the planned treatment. • Per protocol set 1 (PPS1) will include all subjects in FAS1 without any major protocol deviation. • Safety set 1 (SS1) will include all subjects who have received at least one dose of study drug. SS1 will determine the treatment groups based on the actually received treatment. • PK set 1 (PKS1) will include subjects in randomization set 1 who have received at least one dose of CBP-201 active drug and had at least 1 collected and analyzable PK sample. After all subjects (including approximately 81 additional subjects enrolled) entering Stage 2 have completed the treatment, evaluations and follow-up of Stage 2, a Stage 2 analysis will be performed. The Stage 2 analysis is defined as the following 6 analysis populations: • Randomization set 2 will include all subjects entering Stage 2, including all subjects who are randomized into Group C or Group D, and subjects entering Group E. • Full analysis set 2 (FAS2) will include all subjects in randomization set 2 who have received at least one dose of study drug in Stage 2. FAS2 will determine the treatment groups based on the planned treatment. • Per protocol set 2 (PPS2) will include all subjects in FAS2 without any major protocol deviation. • Safety set 2 (SS2) will include all subjects in randomization set 2 who have received the at least one dose of study drug in Stage 2. SS2 will determine the treatment groups based on the actually

	received treatment. • Safety set 3 (SS3) will include all subjects in SS1 and SS2 who have received at least one dose of the study drug. • PK set 2 (PKS2) will include subjects who have received at least one dose of CBP-201 active drug in Stage 2 and had at least 1 collected and analyzable PK sample. **Statistical analysis methods** Statistical analyses will be performed using SAS 9.4 or higher version. Descriptive statistics will be used to summarize the safety, PK, and PD data. Descriptive statistics will include the number of observed subjects, the number of subjects with missing observations, mean, standard deviation (SD), standard error, minimum, median and maximum, frequency, and percentage. For lognormally distributed data, the geometric mean, geometric standard deviation and geometric coefficient of variation will be calculated. Demographic characteristics and baseline characteristics will be listed and summarized. After the 255 subjects enrolled based on the V2.1 and prior versions of the protocol complete the administration and treatment, related evaluations, and follow-up of Stage 1 (W16 pre-dose visit), the primary analysis will be performed, in which the W16 data will be unblinded and statistically analyzed. The primary efficacy endpoint—the proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W16 will be analyzed by stratified CMH Chi-square test, and the estimation of 95% confidence interval for inter-group difference will be provided. The statistically significant type I error level of the primary efficacy endpoint analysis is set at 0.05 (two-sided test). In order to control the probability of multiple comparison type I errors, a fixed-sequence method will be used. First of all, the treatment group and the placebo group will be compared for the primary efficacy endpoint; when the efficacy at the primary efficacy endpoint reaches statistical significance, the treatment group and the placebo group will be compared for the key secondary efficacy endpoints according to the set sequence in the protocol. Statistical inference will not be performed during the Stage 2 analysis. Efficacy analysis: The primary efficacy endpoint will be analyzed by stratified CMH Chi-square test, and the estimation of 95% interval for inter-group difference will be provided. Continuous efficacy endpoints will be summarized by treatment group using descriptive statistics, and comparisons between groups will be performed using Mixed-Effect Model for Repeated Measure (MMRM). The secondary efficacy endpoint analysis will be performed using the same method as the primary efficacy endpoint analysis. Safety analysis: Safety data will be summarized using frequency tables (counts and percentages) and presented by treatment and scheduled time if applicable. AEs will be classified with the Medical Dictionary for Regulatory Activities (MedDRA) terms. If applicable, descriptive statistics will be used to summarize safety data by treatment and scheduled time. The data will be compared with the reference range provided to check for abnormalities and/or clinically relevant changes from baseline (where applicable). PK analysis: If applicable, descriptive statistics will be used to summarize individual blood drug concentrations by treatment and scheduled time, or plot

	a curve of means over time. PD analysis: Descriptive statistics will be used to summarize changes in serum IL-4, IL-13, IgE, TARC levels and peripheral blood eosinophil counts by treatment and scheduled time, and where applicable, plot the mean and SD change curves in each treatment group. The complete details of statistical analysis and methods (including data specifications) will be introduced in a separate Statistical Analysis Plan (SAP), in which PK and PD analyses will be described separately in PK/PD SAP. **Interim analysis** No interim analysis is planned for this study.

1.1. Study Design Diagram

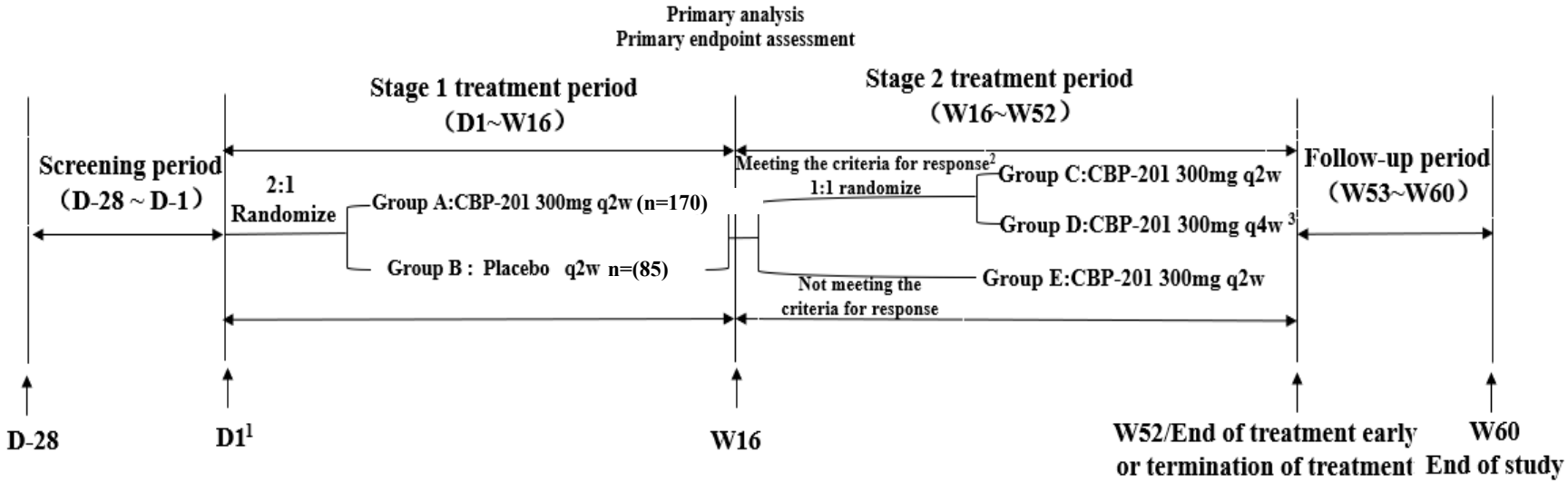


Figure 1: Study Design Diagram

Note:

1. The subjects will receive a loading dose of the study drug (investigational product/placebo) on D1 at a dose of 600 mg (4 ml);
2. Response is defined as a 50% or more decrease in the EASI score;
3. In order to maintain the injection every 2 weeks blind, when not receiving CBP-201, the subjects will receive an injection of placebo 2 ml once every 4 weeks until W52.
4. If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.

1.2. Study Flow Chart

Table 1.1 Screening Period + Stage 1 Treatment Period Flow

Assessment	Screening period D-28~D-1	Stage 1 treatment period									
		D1 Pre-dose	D1 Post-dose	D15 W2 (±3d)	D29 W4 (±3d)	D43 W6 (±3d)	D57 W8 (±3d)	D71 W10 (±3d)	D85 W12 (±3d)	D99 W14 (±3d)	D113 W16 pre-dose (±3d)
Informed consent[1]	√										
Demographic characteristics	√										
Medical history[1]	√										
Inclusion and exclusion criteria[1]	√	√									
Height	√										
Weight	√	√			√		√		√		√
Physical examination[2]	√										√
Vital signs [3]	√	√	√	√	√	√	√	√	√	√	√
12-lead ECG	√	√									√
Chest X-ray	√										
Eye examination[4]	√	√		√	√	√	√	√	√	√	√
Hepatitis and HIV screening[5]	√										
Safety laboratory tests[6]	√	√		√	√		√				√
Pregnancy test[7]	√	√			√		√		√		√
FSH test[8]	√										
PK blood sample[9]		√		√	√		√		√		√
PD blood sample[9]		√		√	√		√		√		√
ADA[10]		√		√	√		√		√		√
Investigator's efficacy assessment[11]	√	√		√	√		√		√		√
Patient reported outcomes[12]	√	√		√	√	√	√	√	√	√	√
PP-NRS[13]	√	√		√	√	√	√	√	√	√	√
Randomization[14]		√									√
SC administration of study drug[15]			√	√	√	√	√	√	√	√	
Injection site assessment[16]			√	√	√	√	√	√	√	√	√
AE[17]	√	√	√	√	√	√	√	√	√	√	√
Prior and concomitant medication/treatment	√	√	√	√	√	√	√	√	√	√	√

Table 1.2 Stage 2 Maintenance Treatment Period + Follow-up Period Flow (Including Unscheduled Visit + Early Termination)

Assessment	Stage 2 maintenance treatment period																		Follow-up visit		Unscheduled visit[17]	ET[18] +7d
	D113 W16 post-dose (±3d)	D127 W18 ±3d	D141 W20 ±3d	D155 W22 ±3d	D169 W24 ±3d	D183 W26 ±3d	D197 W28 ±3d	D211 W30 ±3d	D225 W32 ±3d	D239 W34 ±3d	D253 W36 ±3d	D267 W38 ±3d	D281 W40 ±3d	D295 W42 ±3d	D309 W44 ±3d	D323 W46 ±3d	D337 W48 ±3d	D351 W50 ±3d	D365 EOT W52 ±3d	D393 W56 ±3d	EOS D421 W60 ±3d		
Weight			√		√		√		√		√		√		√		√		√	√	√		√
Physical examination[2]																			√		√	√	√
Vital signs[3]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
12-lead ECG																			√		√		√
Eye examination[4]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
Safety laboratory tests[6]					√				√				√				√				√		√
Pregnancy test[7]			√		√		√		√		√		√		√		√		√	√	√		√
PK blood sample[9]			√		√		√		√		√		√		√		√		√	√	√		√
PD blood sample[9]			√		√		√		√		√		√		√		√		√	√	√		√
ADA[10]			√		√		√		√		√		√		√		√		√	√	√		√
Investigator's efficacy assessment[11]			√		√		√		√		√		√		√		√		√	√	√		√
Patient reported outcomes[12]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
PP-NRS[13]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
SC administration of study drug[15]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√					
Injection site assessment[16]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	√
AE[17]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medication/treatment	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Abbreviations: AD=atopic dermatitis; ADA=anti-drug antibody; AE=adverse event; DLQI=Dermatology Life Quality Index; EASI=eczema Area and Severity Index; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET: early termination; FCBP=female of childbearing potential; HIV=human immunodeficiency virus; HR=heart rate; ICF=informed consent form; IGA=validated investigator global assessment; PD=pharmacodynamics; PK=pharmacokinetics; PP-NRS=Peak Pruritus Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; SAE=serious adverse event; SC=subcutaneous injection; SCORAD=Scoring Atopic Dermatitis Index; VS=vital signs.

Footnotes

1. Before D1 administration of study drug, it must be reconfirmed that the subject has signed the ICF and is eligible for selection. The medical history should also be reviewed before D1 administration.
2. A complete physical examination (PE) is required at screening, W16, W52, EOS/ET and unscheduled visits. The items included are as follows: general appearance, skin, eyes/ears/nose/throat, head and neck, cardiovascular system, respiratory system, abdomen, limbs, lymph nodes, musculoskeletal and nervous systems. Unless it is necessary to assess the status of AD involvement, there is no need to perform rectal or genital examinations. Priority physical examinations can be performed at visits where PE are not scheduled. Attention should be paid to the AD involvement areas and assessment of any AE.
3. Vital signs (VS) include body temperature, respiratory rate, blood pressure, and heart rate. In the Stage 1 treatment period, on D1 and at W2 and W4, VS should be monitored every hour (±10 min) pre-dose and during the 2-hour monitoring period post-dose; from W6 to W14, VS should be monitored pre-dose and 30 min (±10 min) post-dose. In the Stage 2 maintenance treatment period, VS should be monitored every hour (±10 min) pre-dose and during the 2-hour monitoring period post-dose at W16, W18, and W20; from W22 to W50, VS should be monitored pre-dose and 30 (±10 min) min post-dose. During the follow-up period, VS should be monitored at each visit.
4. Eye examination: At each visit, the investigator must assess whether the subject has any eye discomfort, such as redness, itching, photophobia and abnormal discharge, as well as related signs/symptoms, such as conjunctival hyperemia and exudate. If these discomforts are considered to be related to conjunctivitis or keratitis or any uncertain diagnosis, an ophthalmologist should conduct further assessment and give appropriate treatment.
5. Hepatitis screening: Hepatitis B surface antigen, core antibody, HBV-DNA and hepatitis C antibody, HCV-RNA.
6. Safety laboratory tests: Including hematology, blood biochemistry and urinalysis. See Table 9.1 for safety laboratory tests; the test results within 7 days before baseline can be accepted for D1, and there is no need to repeat the test. If the test is performed on the treatment day, samples need to be collected for laboratory tests before administration.
7. For all female subjects of childbearing potential (FCBP), a blood pregnancy test should be performed during the screening period and a urine pregnancy test should be performed on D1 and every 4 weeks thereafter. The test results within 7 days before baseline can be accepted for D1, and there is no need to repeat the test.
8. FSH test: Only for menopausal female subjects; subjects who can provide FSH test results before the screening visit do not need to repeat the test.
9. The trough-concentration (pre-dose) PK/PD samples should be collected (D1, W2, W4 and every 4 weeks thereafter, until W16; once every 8 weeks at W20 and thereafter, until W52); PK/PD samples should also be collected at the early termination visit and follow-up period (W60); among them, blood samples will not

be collected for PD parameter—peripheral blood eosinophils at W12, W20, W28, W36, W44, W52; the collection date and time of each sample will be recorded.

10. If ADA is positive, NAb analysis is also required.
11. Investigator assessments before administration include EASI, IGA, BSA, and SCORAD. If possible, the investigator assessment of the individual subject should be performed by the same person.
12. Patient reported outcomes includes DLQI and POEM, which are assessed once a week. The investigator will dispense the subject diary at each visit and collect DLQI and POEM data of that day, and the data among two visits will be assessed by the subjects themselves and recorded in the subject diary. Old diaries dispensed last time will be collected at the next visit and the new ones will be dispensed. DLQI score will only be assessed among subjects ≥16 years.
13. The PP-NRS (Daily Pruritus Diary) will be distributed at the beginning of the screening and will be reviewed by the study staff at baseline (D1). Baseline PP-NRS must be completed during the screening period, and subjects should complete the daily records within 7 days before the baseline visit (*in these 7 days, the scores of at least 4 days are required for the calculation of the baseline average score. If the patient's reporting days are less than 4 days in the 7 days before the planned date of randomization, randomization should be postponed until the requirements are met, but it is not allowed to exceed the maximum screening period of 28 days*) to determine the baseline severity of pruritus before treatment. During the study period, subjects should record the PP-NRS score of the maximum pruritus intensity in the past 24 hours in the subject's daily diary.
14. Randomization: Two randomizations will be conducted during this study:

- First time: After subjects complete the screening period and meet the inclusion criteria after D1 pre-dose assessment, they can be randomized to Group A (CBP-201 300 mg Q2W) or Group B (placebo Q2W) in a 2:1 ratio before D1 administration;
- Second time: Subjects who are assessed to have achieved EASI-50 before W16 administration will be randomized to Group C (CBP-201 300 mg Q2W) or Group D (CBP-201 300 mg Q4W) in a ratio of 1:1.

15. Unless otherwise stated, all study assessments and examinations should be completed before administration of study drug at each visit. The injection site should be rotated: the abdomen (avoid the area near the umbilicus), the outer thigh, and the upper arm (outer or posterior lateral).
16. The assessment of the injection site will be performed using the injection site response evaluation criteria (Appendix H) provided to each study site. A clinically significant response judged by the investigator will be reported as an AE. At the visit of dosing day, the previous injection site should be assessed before administration (except D1), and the new injection site should be assessed before the subject leaves the study site; only the previous injection site is assessed at the visits when no drug is administered.
17. AEs (the AEs collected before the signing of the ICF to D1 are recorded as pre-treatment adverse events [PTAE]) and SAEs will be collected from the signing of the ICF. AEs and AEs of special interest (AESI) will be collected at each study visit.
18. Unscheduled visits (UV) or the ET visit can be conducted at any time. UV can be conducted for reasons such as AE or disease progression assessment. The investigator can decide which assessments are suitable for an UV, but at least VS and PE (including injection site assessment) should be performed, and the subject should be asked whether any AE has occurred and whether there are new concomitant medications or treatments. If a subject has ET for any reason, an

ET visit should be completed within 7 days after ET to determine the cause of ET, and such assessments should be conducted under the assumption that subject is willing to return to the study site to undergo the end-of-study assessment procedures. It should be noted that ET subjects should also try their best to complete the 8-week follow-up visit after the last dose of study drug.

2. Table of Contents

2.1. List of Tables

3. List of Abbreviations and Definitions of Terms

Abbreviations	Terms
AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKC	Atopic Keratoconjunctivitis
ANCOVA	Analysis of Covariance
AUC	Area Under the Concentration-Time Curve
AUC_{last}	The Area Under the Concentration-Time Curve from the Zero Time Point to the Last Time Point
BP	Blood Pressure
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
C_{max}	Maximum Blood Concentration
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
D# or D-#	Day # (the date in the study), Day -# (before the start of treatment)
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
FCBP	Female of Childbearing Potential
FDA	U.S. Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
H/h	Hour
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for

Abbreviations	Terms
	Registration of Pharmaceuticals for Human Use
IGA	Validated Investigator Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-13	Interleukin-13
IL-4Rα	Interleukin-4 Receptor Alpha
IUD	Intrauterine Contraceptive Device
JAK	Janus Kinase
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MMRM	Mixed Model Repeated Measures
NAb	Neutralizing Antibody
NCS	Not Clinically Significant
PD	Pharmacodynamics
PDE-4	Phosphodiesterase-4
PE	Physical Examination
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
P-NRS	Pruritus Numerical Rating Scale
POEM	Patient Oriented Eczema Measure
PTAE	Pre-treatment adverse event
PP-NRS	Peak Pruritus Numerical Rating Scale in the past 24 hours (0-10)
PPS	Per Protocol Set
PRO	Patient Reported Outcome
Q2W	Once Every 2 Weeks
Q4W	Once Every 4 Weeks
QA	Quality Assurance
QOL	Quality Of Life
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous Injection
SCORAD	Scoring Atopic Dermatitis Index
SD	Standard Deviation
SIT	Allergen-specific Immunotherapy
SOC	System Organ Class
SS	Safety Set

Abbreviations	Terms
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Elimination half-life
TARC	Thymus Activation Regulatory Chemokine
TB	Tuberculosis
TCI	Calcineurin Inhibitor
TCM	Traditional Chinese Medicine
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
vIGA-AD™	Validated Investigator Global Assessment for Atopic Dermatitis
VKC	Vernal Keratoconjunctivitis
W#	Visit in Week # after the start of treatment
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

4. Introduction

4.1. Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects millions of patients worldwide. AD usually develops in childhood, most commonly in infancy. Two-thirds of patients have the onset before the age of 2, but AD may also develop in subsequent stages [2]. However, a recent study carried out in a Chinese hospital reported that 77.5% of the 2662 patients had the onset after 12 years of age [3]. AD afflicts 15%-20% of children [2], and is less common in adults than children (the point prevalence rate is 1.6%-11.5%, but there are great differences between different countries or regions) [1, 4]. In addition to other annoying symptoms, the main features of AD are intense pruritus and recurring eczematous skin lesions [5]. The resultant sleep disturbance, persistent pruritus and social distress can cause depression and other psychological disorders [6, 7, 8, 9, 10].

The pathophysiology of AD is very complex, involving the interactions of skin barrier function, genetics, environmental factors, and immune response. The skin barrier function of AD patients will decrease, and the loss of water through the skin will increase. Local inflammation and scratching trauma can lead to further destruction of barrier function and further deterioration of infection [11, 12, 13, 14]. Atopic family history is closely related to the onset of AD, and so is the loss of filaggrin gene mutation [15]. Regarding immune disorders, the excessive activation of T cells accompanied by skin infiltration caused by T cells and dendritic cells is a sign of AD [14]. Interleukin (IL)-4, IL-5, IL-13 and IL-31 and other T helper cell cytokines are related to the pathophysiology of AD [16]. Therapies targeting cytokines are an active area of research and drug development [17].

The diagnosis of AD is based on clinical manifestations and diagnostic guidelines. Diagnostic guidelines such as Hanafin and Rajka criteria have been used in clinical practice and research [1]. The Hanafin and Rajka criteria require a comprehensive consideration of primary criteria (e.g., pruritus, chronic dermatitis, and history of respiratory/skin allergies) and secondary criteria (e.g., facial paleness, periorbital dark areas, environmental or food triggers) to diagnose AD. No specific laboratory or histopathological findings related to AD have yet been found, but AD is sometimes associated with increased levels of immunoglobulin E and eosinophil counts [18, 19, 20].

Topical drugs, such as emollients and corticosteroids, are often used in the treatment of AD [21]. Other topical medications include calcineurin inhibitors, such as tacrolimus, antibiotics and phosphodiesterase inhibitors [22]. There are limitations in the use of topical drugs, such as limited efficacy, various reactions at the site of administration, limited sites of administration, and possibility of complications caused by long-term use (corticosteroids, calcineurin inhibitors) [23]. Systemic therapy drugs include antibiotics, corticosteroids, cyclosporine, and methotrexate, but the existing systemic therapy drugs have great limitations, such as insufficient efficacy, and safety issues such as adrenal suppression, Cushing's syndrome, and

organ toxicity and cancer risks [24, 25, 26]. Dupilumab is a monoclonal antibody against IL-4 receptor α. It has been approved in the United States for the treatment of moderate to severe AD in adult (2017) and adolescent (2019) patients when topical therapeutic drugs cannot adequately control the disease; it has been approved in China for the treatment of moderate to severe AD in adults whose disease is not well controlled with topical prescription drugs or for whom the use of topical prescription drugs is not recommended; similar indications have also been approved in other countries or regions [27, 28, 29].

CBP-201 is a human IgG4κ monoclonal antibody against IL-4 receptor α. Like dupilumab, CBP-201 can block the signaling pathways of IL-4 and IL-13 which play an important role in the pathogenesis of AD. Preclinical studies have proven that CBP-201 has ideal pharmacological characteristics, higher affinity and specificity for the target, higher potency and longer half-life compared with dupilumab. CBP-201 is currently being developed for the treatment of AD, and is planned to be developed for other indications, such as asthma and other inflammatory diseases.

4.2. Physical, Chemical and Pharmacological Properties

CBP-201 is a recombinant fully human monoclonal antibody that can bind to human interleukin-4 receptor α (IL-4Rα), that is, the common subunit of interleukin 4 (IL-4) and interleukin 13 (IL-13) receptor dimers. It is a human IgG4 containing κ light chain, and the protein molecular weight is about 146.45 kDa. The amino acid Ser223 in the Fc region of the heavy chain has been mutated to Pro223 to promote the stability of the molecule.

CBP-201 injection is a clear to slightly opalescent, colorless to pale yellow liquid. The container is a vial whose strength is 150 mg (1 ml)/vial, which can be directly used for administration. The CBP-201 injection preparation contains a variety of excipients, including L-histidine, NaCl, trehalose and Tween 80. The placebo control solution contains the same excipients as the CBP-201 injection, but does not contain the CBP-201 active drug.

4.3. Preclinical Studies

Preclinical data [31] has proven that CBP-201 has ideal pharmacological characteristics, and has high affinity and specificity for antigens. Therefore, compared with dupilumab, the potency is higher, with a longer half-life. At present, a large number of in vitro studies have been carried out to characterize the pharmacological properties of CBP-201. CBP-201 has a high affinity for soluble recombinant human IL-4Rα and can inhibit the proliferation of erythroleukemia (TF-1) cells. In addition, CBP-201 can also inhibit the activation of IL 4 and IL 13 mediated signal transducer and activator of transcription 6 (STAT6) in human embryonic kidney (HEK) BlueTMIL-4/IL-13 SEAP cells. In vitro test results show that CBP-201 can inhibit the production of IL-4 and IL-13-induced thymus activation regulatory chemokine (TARC, also known as CCL17) and MDC (chemokine derived from human macrophages [CCL22]) in human peripheral blood mononuclear cells. These studies indicate that CBP-201 is an antibody with high affinity for IL 4Rα. The PK characteristics of CBP-201 have been studied in mice

and monkeys, and excellent dose proportionality has been observed at three dose levels, indicating that it has good bioavailability.

Similar to other similar drugs (e.g., dupilumab), CBP-201 does not cross-react with IL-4Rα in preclinical species (mouse, rat, monkey). Therefore, the toxicity of CBP-201 in inhibiting IL-4Rα cannot be directly assessed in these animals. Connect conducted a 4-week monkey toxicology study to assess the potential off-target toxicity of CBP-201 to support the first-in-human single-dose study in healthy volunteers. In this study, cynomolgus monkeys were injected SC with CBP-201 at doses of 6 mg/kg, 40 mg/kg and 200 mg/kg, once a week, with a total of 4 injections. The results showed that the tolerability was good. The no observed adverse effect level (NOAEL) of CBP-201 was 200mg/kg, the corresponding maximum blood concentration (C_{max}) was about 6279μg/mL, and the area under the concentration-time curve (AUC_{last}) from zero time point to the last measurable concentration after the last dose was about 837.4 h*mg/mL. In this study, there were no clinically significant changes in clinical observation results, gross observation results, coagulation, clinical biochemistry, hematology, lymphocyte count, plasma complement, or cytokine levels.

4.4. Clinical Studies

4.4.1. Phase I Single Ascending Dose Study

A single ascending dose (SAD) study of CBP-201 has been completed in 40 healthy adult subjects (Connect study CBP-201AU001) [30]. The subjects in 4 dose groups (75 mg, 150 mg, 300 mg and 600 mg) received a subcutaneous injection of CBP-201 or placebo, and the subjects in another dose group received an intravenous injection of CBP-201 or placebo 300 mg. After the administration was completed, subjects in all dose groups were followed up for 12 weeks to assess the safety, tolerability, PK and PD characteristics of the drug. In all treatment groups, 31 out of a total of 40 subjects had at least 1 TEAE. Among all subjects who received CBP-201 administration, 80.0% had at least 1 TEAE; among all subjects who received placebo administration, 70.0% had at least 1 TEAE. The frequency of TEAE did not increase with the increase of CBP-201 dose. In all treatment groups, the most common TEAEs were various neurological symptoms and infectious diseases. The most common AEs were headache (subjects in all CBP-201 groups, 53.3%; subjects in all placebo groups, 30.0%) and upper respiratory tract infection (combined CBP-201 group subjects, 33.3%; placebo group subjects, 40.0%). Injection site reactions were uncommon, with single episodes of injection site pain (CBP-201 75 mg SC), injection site paresthesia (CBP-201 300 mg SC), and injection site bruises. In general, CBP-201 had good safety and tolerability. All AEs in the study were mild to moderate, no SAEs, no AEs related to abnormal laboratory tests or ECG abnormalities occurred, and no AEs resulted in early withdrawal from the study. The most common treatment-emergent adverse events (TEAE) and TEAEs related to the study drug were headache and upper respiratory tract infection. AEs at the injection site were uncommon.

The increase ratio of CBP-201 exposure was greater than the increase ratio of dose, indicating

that the drug is cleared in a non-linear manner, consistent with the clearance of targeted-mediated drugs. Its absolute bioavailability was 58%, and the median time from the zero time point to the last detectable drug ranged from 338 hours (14 days, 75 mg) to 1345 hours (56 days, 600 mg). A single subcutaneous injection of 75 mg to 600 mg of CBP-201 significantly reduced the serum level of thymus activation regulatory chemokine (TARC; also known as CCL-17). The level of CCL-17 in serum can be adjusted by blocking IL-4Rα, so it can be used as a biomarker for judging AD or other related inflammatory diseases.

4.4.2. Phase I Multiple Ascending Dose Study

CBP201 was evaluated in a multiple ascending dose (MAD) study in adult patients with AD [30] (Connect study CBP-201AU002). In this randomized, double-blind, placebo-controlled, multiple ascending dose study, 31 moderate to severe AD patients aged 20 to 65 were enrolled at 13 study sites in Australia and New Zealand. The patients received CBP-201 (SC, 75 mg, 150 mg or 300mg) or matching placebo once a week for 4 consecutive weeks. About 10 patients were randomly enrolled in each dose group and received CBP-201 or placebo treatment in a ratio of 4:1.

In general, CBP-201 had good safety and tolerability when the dose of subcutaneous injection was up to 300mg. No SAE, life-threatening TEAEs, or deaths were reported in the study, and no TEAEs that led to discontinuation of the study were reported. No clinically significant injection site reactions were reported as AEs. The most common AEs during the study period were deterioration of AD (26.1% in the combined CBP-201 treatment group and 37.5% in the placebo group), headache, and upper respiratory tract infection. Most TEAEs were mild.

The number and severity of TEAEs and treatment-related TEAEs did not increase with the increase of CBP-201 dose levels. There were no clinically significant (CS) or study treatment-related changes in vital signs, ECG parameters, or physical examination results.

At the doses of 150 mg and 300 mg, CBP-201 administration for 4 weeks could quickly improve EASI, IGA and PP-NRS. On Day 29, 87.5% (7/8 cases) of the patients in the 150 mg group had a 50% reduction in EASI score (EASI-50), and 100% (7/7 cases) of the patients in the 300 mg group achieved EASI-50, while only 37.5% (3/8 cases) of the patients in the placebo group achieved EASI-50. For IGA, 50.0% (4/8 cases) of the patients in the 150mg group, 42.9% (3/7 cases) in the 300 mg group, and only 12.5% (1/8 cases) in the placebo group had an IGA score of 0-1 (clearance, basic clearance). The average weekly PP-NRS severity was decreased by 41.0% and 52.8% in the CBP-201 150 mg group and 300 mg group, respectively, and by 22.8% in the placebo group. On Day 29, the P-NRS response rates (decreased by >3 points) in the 150 mg (50%, 4/8) and 300 mg groups (57%, 4/7) were higher than that in the placebo group (25%, 2/8).

The results of PK analysis showed that about one week (Day 29) after the 4th administration of CBP-201 on Day 22, the peak concentration of CBP-201 was observed. The dose proportionity assessed based on AUC_{0-t} and C_{max} showed that when the dose was increased from 75 mg to

150 mg, the increase in exposure was greater than the increase in dose; when the dose was increased from 150 mg to 300 mg, the increase in exposure was proportional to the increase in dose.

Serum TARC was decreased steadily after CBP-201 was administered at 150 mg and 300 mg. The decrease in TARC was always related to the improvement of AD.

4.4.3. China Phase Ia Single Dose Escalation Study

A "randomized double-blind, placebo-controlled, single-dose, dose-escalation Phase I clinical study to evaluate the safety, tolerability, PK and PD of CBP-201 in Chinese healthy adult subjects" is being carried out in China to explore the safety, tolerability and PK/PD characteristics of CBP-201 in Chinese healthy adult subjects.

This study sets 3 dose groups, namely 150 mg, 300 mg and 600 mg. It is planned to enroll 36 healthy subjects, both male and female, who will be divided into 3 groups, with 12 cases in each group (among them, 10 cases will receive the study drug CBP-201 and 2 cases placebo). All subjects will continue to be observed at the clinical site for 72 hours after receiving the investigational drug, and PK, PD and ADA samples will be collected to assess AEs and injection site reactions. After more than 8 subjects have completed the observation period of at least 15 days after the single-dose administration, the PI, study doctor, and sponsor's medical monitor will first blindly assess the safety data of this dose group, and then decide whether to administer the drug in the next dose group.

Up to now, the study has successfully completed the enrollment and follow-up of 36 healthy subjects planned for the 3 dose groups, and sample testing and data collection are in progress. In this study, at three blinded safety review committee meetings conducted 15 days after the administration in each dose group, the investigators all agreed that CBP-201 was safe and well tolerated.

4.4.4. Phase II International Multicenter Clinical Study in Patients with Moderate to Severe AD

CBP-201 was evaluated in a Phase 2b, randomized, double-blind, placebo-controlled efficacy and safety study in adult patients (n = 226) with moderate-to-severe AD in Australia, New Zealand, US, and China. Baseline disease characteristics (including duration of AD history, baseline IGA score, total EASI score, and BSA involvement) were generally balanced between the All CBP-201 group and the placebo group. The median age of the overall population was 38.5 years (range18-73 years). Patients were randomized (1:1:1:1) to receive CBP-201 (600 mg loading dose followed by 150 mg Q2W), CBP-201 (600 mg loading dose followed by 300 mg Q4W), CBP-201 (600 mg loading dose followed by 300 mg Q2W), or matching placebo administered SC for 16 weeks and followed with an 8-week post-treatment follow-up.

The safety profile of CBP-201 in this study was generally comparable to that of placebo, with no clinically relevant differences observed between treatment groups. CBP-201 treatment

groups and placebo had a similar incidence of TEAEs, SAEs, and TEAEs leading to discontinuation. The most common TEAEs in the CBP-201 dose groups were atopic dermatitis (15%) and headache (5%); all other TEAEs were reported for ⩽ 2% of CBP-201-treated subjects. Most reported TEAEs were mild to moderate in severity. The proportion of subjects with Grade ⩾ 3 TEAEs was higher in the 300 mg Q4W group than the 150 mg Q2W group, 300 mg Q2W group, or placebo group. One subject in the 300 mg Q4W CBP-201 group experienced a fatal (Grade 5) TEAE of cardiac arrest 57 days after last dose of study drug. There were no clinically relevant trends in clinical safety laboratory (hematology, blood chemistry, and urinalysis) values, vital sign values, ECG findings, or physical examination findings across doses or over time for up to 16 weeks of treatment.

Administration of CBP-201 resulted in rapid improvements in EASI, IGA, and PP-NRS at 16 weeks. All doses of CBP-201 met the primary endpoint (LS mean percent change from baseline in EASI at Week 16 versus placebo), with greater reductions observed in EASI in the 300 mg Q2W and Q4W groups. Significant improvements with CBP-201 were also seen for a range of secondary efficacy endpoints, including proportions of EASI and IGA 0/1 responders and change in PP-NRS. The efficacy responses of 300 mg CBP-201 Q2W and Q4W were more consistently greater than 150 mg Q2W when compared to placebo across most outcomes.

ADA/NAb results

In the 150 mg Q2W dose group, 8 subjects tested positive for ADA. Five of these subjects tested positive at a single timepoint only, either in the middle of the time course (transient, n = 2) or at only the final timepoint (indeterminate, n = 3). Three subjects had persistent ADA, testing positive at two or more consecutive timepoints. Titers were low, with all titers <1000. Six subjects were positive for Nab.

In the 300 mg Q4W dose group, 7 subjects tested positive for ADA. Four of these subjects tested positive at a single timepoint only (transient n = 3; indeterminate n = 1). Three subjects had persistent ADA, testing positive at more than one timepoint. Titers were low, with all but one titer reported as <1000. One subject had a Day 169 (last timepoint collected) titer at 32,000. Five subjects were positive for Nab.

In the 300mg Q2W dose group, 2 subjects tested positive for ADA. One subject (0304-0020) was positive for pre-existing ADA only, with no detection of a treatment boosted ADA (titer did not exceed the initial titer of 160). This subject was positive for NAb. The second subject positive for ADA in this dose group was transiently positive on Day 113, had a titer of <10, and was NAb negative.

In the Placebo dose group, 10 subjects tested positive for ADA. Seven of these subjects were positive at a single timepoint only (transient n = 6; indeterminate n = 1), with titer <10, and NAb negative. As such, they may represent false positives. One subject (0340-0003) had a pre-existing ADA positive/NAb positive response, and subsequent timepoints were also ADA/NAb positive. Titers did not exceed 80. Two subjects showed persistent, treatment-emergent ADA.

One of these subjects, 0304-0014, was ADA/NAb positive at the last 3 timepoints collected, with titers <40. The second subject, 0401-0015, was ADA/NAb positive beginning at Day 29 with all subsequent timepoints also ADA/NAb positive. In this subject, titers were all >1000 (range 1034 to 4825). The treatment-emergent ADA/NAb responses are unusual and unexpected for subjects in a Placebo arm, particularly the subject with high titers. No anomalies in the bioanalysis or other aspects of the study were identified to account for these results.

Overall, there was a low incidence of ADA/NAb and most responses were not persistent. All ADA responses were low titer (<1000) except for 2 subjects (one placebo outlier, one subject in 300 mg Q4W group). The PK analysis indicated that in the allometric model, subjects for whom anti-drug antibodies were present had 15% higher non-saturable clearance than those for whom they were absent.

PK results

The pharmacokinetic analysis demonstrated the need for two elimination pathways, one of which was concentration dependent saturable, consistent with a previous analysis of CBP-201 in healthy subjects and subjects with atopic dermatitis. The concentration at which the saturable pathway was 50% inhibited was 164 – 184 ng/mL, a value lower than typical trough concentrations seen with multiple dosing in the present study. As a result, saturable clearance is unlikely to influence the concentration profile of CBP-201 in clinical practice. .

Body size was incorporated into the model using two approaches: allometric scaling and weight normalized scaling. After incorporation of other covariates, these scaling approaches yielded similar fits. However, the model with allometric scaling showed the least amount of bias in the relationship between post hoc etas for non-saturable clearance and weight.

Chinese subjects had up to 23% lower bioavailability than non-Chinese subjects. Distinguishing whether these differences in exposure between Chinese and non-Chinese subjects results from bioavailability or clearance differences between these two populations is difficult in the presence of sparse sampling. Regardless, both approaches suggest that systemic exposure is lower in Chinese subjects. It should be noted that bioanalysis for samples from China was performed in a different laboratory (Frontage) compared to ex-China samples (Syneos). Although assay comparability between the two laboratories was established, these data should be reviewed, and conclusions made, with that in mind.

Both clearance pathways increased with increasing baseline neutrophil or white blood cell counts. Simulation showed that over the range of neutrophil counts observed in the study, exposure ranged approximately 2-fold.

Finally, in the allometric model, subjects for whom anti-drug antibodies were present had 15% higher non-saturable clearance than those for whom they were absent. ADA was not incorporated into the models using the other scaling approach.

Simulations of fixed dose and weight-proportional dose regimens suggested that there would

be no advantage in terms of exposure variability in switching from a fixed to a weight-based dose.

Simulations based on region (China or ex-China) suggested approximately 25% lower exposure in Chinese subjects compared to non-Chinese subjects.

Simulations based on post hoc parameter estimates and actual dosing history suggest that 300 mg Q2W maintained the highest C_{trough}, C_{max}, and C_{mean}. Of the remaining two regimens, 300 mg Q4W maintained the higher C_{max} and the lower C_{trough}. C_{mean} was similar for 150 mg Q2W and 300 mg Q4W.

Exposure-response

Investigator ratings consistently showed that increasing exposure, best assessed by mean concentration during the first or final dosing interval, was associated with a larger response. In most instances, there were no differences between treatment groups. Lighter subjects had larger values for some exposure metrics (e.g., mean concentration during the first dosing interval); for some response metrics, this resulted in these subjects having a larger response compared to heavier subjects. For EASI, the response in Chinese subjects was larger compared to ex-China.

Of the patient ratings, POEM yielded the best relationship between increasing exposure and response. The relationship for DLQI was inconsistent between exposure metrics. For PP-NRS, there was no evidence of an association between exposure and response.

The five biomarkers failed to yield a consistent exposure-response relationship. For each of these biomarkers, the presence of outlier values at baseline and later timepoints may have limited the ability to detect an exposure-response relationship..

The primary efficacy endpoint for this study was EASI, for which a strong exposure-response relationship was apparent.

4.5. Other Safety Considerations

The current clinical experience of CBP-201 is limited. Given that dupilumab is a similar product that has been marketed and binds to the same target (IL-4Rα), examples of existing safety observations include but are not limited to the following:

- Hypersensitivity reactions (e.g., urticaria, rash, erythema nodosa, immediate severe allergic reactions, serum sickness);
- Eosinophilic disease (e.g., systemic eosinophilia, sometimes manifested as eosinophilic pneumonia or clinical features of vasculitis consistent with eosinophilic granulomatous polyangiitis, worsening of pulmonary symptoms, cardiac complications and/or neuropathy in patients with eosinophilia);
- Reactions caused by reduced doses of glucocorticoids (abrupt discontinuation of systemic, local or inhaled glucocorticoids may be related to systemic withdrawal symptoms and/or the appearance of symptoms previously suppressed by systemic

glucocorticoid therapy);

- Injection site reactions;
- Oropharyngeal pain;
- Eosinophilia;
- Conjunctivitis, including allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation and eye inflammation;
- Blepharitis;
- Oral herpes;
- Keratitis, including ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis and ocular herpes simplex;
- Itchy eyes;
- Other herpes simplex virus infections, including genital herpes, herpes simplex otitis externa and herpes virus infections;
- Dry eye;
- Joint pain;
- Gastritis;
- Insomnia;
- Toothache.

4.6. Study Rationale

As mentioned above, it can be seen from the results of Phase Ia and Ib clinical studies completed in Australia and New Zealand that in healthy subjects, a single subcutaneous injection of CBP-201 75 mg, 150 mg, 300 mg and 600 mg and intravenous injection of 300 mg or subcutaneous injections of 75 mg, 150 mg and 300 mg once a week for 4 times in patients with moderate to severe AD have good safety and tolerability. At the same time, in patients with moderate to severe AD, CBP-201 150 mg and 300 mg injected subcutaneously every week demonstrated preliminary clinical efficacy, and the changes in TARC, a biomarker related to AD severity, showed a consistent trend with the improvement of the disease. At the same time, there was no significant difference in TEAEs between each dose group and the placebo group. These study results support further research on the therapeutic effects of CBP-201 on AD. At the same time, the ongoing Phase I study of a single subcutaneous injection of CBP-201 150 mg, 300 mg and 600 mg in healthy Chinese subjects has completed enrollment and follow-up, and at three blinded safety review committee meetings conducted 15 days after the administration in each dose group, the investigators all believed that CBP-201 was safe and well tolerated, supporting the continued clinical development of CBP-201 in China. Therefore,

this study is planned to further assess the efficacy, safety and PK characteristics of CBP-201 in patients with moderate to severe AD in China.

Compared with adults, the prevalence of AD is significantly higher in children and adolescents [1,2,4], and the treatment options available for children and adolescents aged 12 years and above are more limited. For children with moderate to severe AD, in particular, there is still a huge unmet clinical need. CBP-201 has demonstrated good safety, tolerability and efficacy in previously completed clinical studies, and the marketed same-target (IL-4Rα) product dupilumab has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of moderate to severe AD in children aged 6-11 years and adolescents aged 12 years and above, and also been approved in China for the treatment of moderate to severe AD in adolescents aged 12 years and above. The safety and efficacy data of dupilumab in pediatric AD patients have provided strong support for the rationality and feasibility of clinical studies of CBP-201 in the pediatric population, that is, no unique pediatric safety issues have been observed with the marketed medicinal product of the same class sharing the same target as CBP-201 (IL-4Rα), and the efficacy in the pediatric population is definite. In order to encourage and facilitate the research and development of medicinal products for the pediatric population, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has formulated ICH E11 (R1), a specific guideline for the clinical studies of medicinal products for the pediatric population (including adolescents aged 12 years and above). With regard to the timing of the initiation of pediatric studies during the research and development of a medicinal product, ICH E11 (R1) recommends that factors such as the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments should be comprehensively considered. In cases where the medicinal product will be used in pediatric patients but the disease to be treated is not urgent, ICH E11 (R1) recommends that testing of these medicinal products in pediatric populations can usually begin at clinical phase 2 or 3 (Section 2.3.3). For medicinal products intended to treat serious or life-threatening diseases, occurring in both adults and pediatric patients, for which there are currently no or limited therapeutic options, ICH E11 (R1) recommends that medicinal product development should begin early in pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit (Section 2.3.2). In conclusion, this study plans to enroll certain number of adolescents with moderate to severe AD aged 12 years and above under the premise of meeting the requirements of the ICH E11 (R1) guideline. The safety and efficacy data of adolescent AD patients obtained in this study will provide an important reference for further design and conduct of clinical studies in younger pediatric populations in the future.

The treatment in this study is divided into two stages. Stage 1 is a placebo-controlled design (subjects will receive CBP-201 600 mg or placebo SC administration on D1, and start to receive CBP-201 300 mg or placebo administration Q2W starting from Week 2); Stage 2 is the maintenance treatment period with different dosing regimens of CBP-201 (CBP-201 300 mg,

Q2W or Q4W).

5. Study Objectives

5.1. Primary Objective

- To assess the efficacy of CBP-201 in subjects with moderate to severe AD

5.2. Secondary Objectives

- To assess the safety and tolerability of CBP-201 in subjects with moderate to severe AD
- To assess the PK characteristics of CBP-201 in subjects with moderate to severe AD
- To assess the PD characteristics of CBP-201
- To assess the immunogenicity of CBP-201

6. Study Plan

6.1. Overall Study Design and Plan

This study is a randomized, double-blind, multi-center, controlled study designed to assess the efficacy, safety and PK characteristics of CBP-201 in eligible subjects with moderate to severe AD.

The study includes a screening period, a treatment period and a follow-up period. The treatment period is divided into two stages:

Stage 1 study: It is a placebo-controlled study, in which subjects who meet the inclusion criteria and do not meet the exclusion criteria will be stratified according to the severity of their baseline disease (moderate [IGA=3] and severe [IGA=4]) and randomized into one of the following 2 groups to receive investigational product or placebo treatmentby the ratio of 2:1:

- Group A (CBP-201): the subjects will receive a subcutaneous injection of CBP-201 600 mg (4 ml in total, 2 injections of 2ml each in different sites) on Day 1, begin to receive a subcutaneous injection of CBP-201 300 mg (2 ml) from Week 2 (W2), and receive treatment at the same dose every 2 weeks thereafter until W14;
- Group B (placebo): the subjects will receive a subcutaneous injection of placebo 4 ml (2 injections of 2ml each in different sites), begin to receive a subcutaneous injection of placebo 2 ml from W2, and receive placebo 2 ml every 2 weeks thereafter until W14.

The grouped dosing regimen in Stage 1 is shown in the table below:

Table 6.1 Grouped Dosing Regimen in Stage 1

Group	W0	W2	W4	W6	W8	W10	W12	W14
Group A	4XC	2XC	2XC	2XC	2XC	2XC	2XC	2XC
Group B	4XP	2XP	2XP	2XP	2XP	2XP	2XP	2XP

Note: C=CBP-201; P=placebo; #X=number of ampoules

Before the administration of study drug at W16 visit, all subjects will be assessed for efficacy, and treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in EASI score (ie EASI-50).

Stage 2 study: The grouping for Stage 2 maintenance treatment is as follows:

- Subjects who have achieved EASI-50 in the W16 pre-administration treatment assessment will be 1:1 randomized to one of the following two groups to receive study treatment starting from W16:
  - Group C: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 2 weeks until W50;
  - Group D: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 4 weeks. In order to maintain the injection every 2 weeks blind, when not

receiving CBP-201, the subjects will receive an injection of placebo 2 ml once every 4 weeks until W50.

- Subjects who have not achieved EASI-50 in the W16 pre-administration treatment assessment will receive the following treatment starting from W16:
  - Group E: The subjects will receive a subcutaneous injection of CBP-201 300 mg every 2 weeks until W50.
- If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.

The grouped dosing regimen in Stage 2 is shown in the table below:

Table 6.2 Grouped Dosing Regimen in Stage 2

Group	W16	W18	W20	W22	W24	……	W50
Group C	2XC	2XC	2XC	2XC	2XC	……	2XC
Group D	2XC	2XP	2XC	2XP	2XC	……	2XP
Group E	2XC	2XC	2XC	2XC	2XC	……	2XC

Note: C=CBP-201; P=placebo; #X=number of ampoules

During the study period, subjects must apply a mild emollient to the AD-affected area at least twice a day as background treatment (but should avoid using emollients within 4 hours before AD assessment at each visit.

All subjects (including the subjects who are early terminated of the treatment) will be followed up for 8 weeks after the last dose.

In this study, an independent DSMB will be established to regularly review and evaluate the cumulative study data, to guarantee the safety of subjects, implementation and progress of the study, and to give the sponsor a suggestion on whether to continue the study.

The overall study design is shown in Figure 1.

6.2. Study Steps

The study consists of a screening period, a treatment period (including Stage 1 treatment [16 weeks] and Stage 2 maintenance treatment [36 weeks] and a follow-up period (8 weeks).

After signing the ICF, subjects will be assessed for study eligibility at the screening visit within 28 days prior to the baseline visit. Before D1 administration of study drug, subjects who were eligible at the screening visit will be confirmed again for their eligibility. After baseline assessment, the subjects who are confirmed to meet the inclusion criteria will be randomized to Group A (CBP-201) or Group B (placebo) in a 2:1 ratio to receive CBP-201 or placebo SC administration. Vital signs monitoring will be conducted at the study site before D1, W2 and W4 administration and 2 hours after administration, and before and 30 minutes after each

administration from W6 to W14.

Before W16 administration, the therapeutic results of all subjects will be assessed, and treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in EASI score (ie EASI-50). Subjects who are assessed to have achieved EASI-50 before W16 administration will be 1:1 randomized to Group C or Group D and start receiving SC administration of CBP-201 300 mg Q2W or Q4W until W50 (*If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration treatment assessments, they will be assigned to group E to be treated with subcutaneous injection of CBP-201 300 mg every 2 weeks from the visit when EASI-50 is not achieved for the second time to W50.*); subjects who are assessed to have not achieved EASI-50 before W16 administration will be assigned to Group E to start receiving SC administration of CBP-201 300 mg Q2W until W50. All subjects should undergo vital signs monitoring before administration and 2 h after administration at W16, W18 and W20 at the study site, and before and 30 min after each administration from W22 to W50. After the end of Stage 2 (W52), subjects will be followed up for safety and efficacy for 8 weeks to further explore the PK and PD characteristics of CBP-201.

Subjects will return to the study site for examinations and assessments according to the time specified in the Study Flow Chart. Various study assessments and examinations should be completed before administration at each visit (unless otherwise specified).

Blood samples from all subjects will be collected during the whole study period to evaluate the steady-state PK characteristics of CBP-201 and its PD effects on serum thymus activation regulated chemokine (TARC) level, total immunoglobulin E (IGE) level, peripheral blood eosinophil count and serum IL-4 and IL-13 levels, and to detect ADA (*all ADA positive samples will be further tested for the presence of anti-CBP-201 NAb*).

During the study period, subjects are also required to apply mild emollients to the AD-affected area at least twice a day (in order to facilitate the assessment of dryness and scales, the use of emollients should be avoided within 4 hours before the assessment) and fill in a daily pruritus diary every day. If an intolerable AD recurrence or worsening of the condition occurs, the subject should notify the study site to assess the condition and confirm whether it is necessary to use rescue drugs for treatment.

Throughout the study period, AE assessment will be continued and concomitant medication/treatment information will be collected.

If a subject has ET for any reason, the subject should complete the ET visit within 7 days after ET, and complete the 8-week follow-up visit as much as possible after the ET visit.

The assessment of the severity and impact of AD will be divided into two parts: the investigator's efficacy assessments and the patient reported outcomes:

1) **Patient reported outcomes (completed by the subject):**

- PP-NRS: It is a single self-reported item designed to measure the peak pruritus or "worst" pruritus in the past 24 hours based on the following questions: "The scores are 0-10, in which 0 represents 'no pruritus' and 10 "worst imaginable pruritus'. How do you rate your most severe puritus in the past 24 hours?" [31]. Refer to Section 17.1, Appendix A. The PP-NRS (Daily Pruritus Diary) will be distributed at the beginning of the screening visit. Subjects will be instructed to complete the PP-NRS (Daily Pruritus Diary) within 7 days before the baseline visit (D1) to calculate the baseline average score of subjects, which will be reviewed by the study staff at the baseline visit (D1). Thereafter (from D1), the daily PP-NRS will be collected every day (in the past 24 hours).
- DLQI: It is a questionnaire containing 10 items to assess the impact of AD on quality of life (QOL) in the past week, and the scores range from 0 (no disease) to 30 (severe disease); the higher the score, the worse the quality of life. Refer to Section 17.2, Appendix B. DLQI score will only be assessed among subjects ≥16 years, and it will be assessed once a week during the study period.
- POEM: It is a questionnaire composed of 7 items to assess disease symptoms on a scale of 0-4 (dryness, itching, flaking off, cracking, sleeplessness, bleeding and weeping or oozing); the scores range from 0 (no disease) to 28 (severe disease); the higher the score, the worse the quality of life. Refer to Section 17.3, Appendix C. It will be assessed once a week during the study period.

2) Investigator's efficacy assessments (completed by the investigator):

- IGA: The Validated Investigator Global Assessment for AD (vIGA-AD™) Scale is a 5-point classification scale based on the overall appearance of the skin lesions at a specific time point (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe). It should be noted that in order to be eligible for selection, the IGA score must be ≥3. See Section 17.4, Appendix D. Please also note that IGA-1 should not contain scales.
- EASI: The EASI scale quantifies the severity and extent of AD, as well as the severity of erythema, infiltration, excoriation and lichenification of the four anatomical regions—head and neck, trunk, upper extremities and lower extremities. The total EASI score ranges from 0 (lowest) to 72 (highest); the higher the score, the higher the severity of AD (more severe). It should be noted that in order to be eligible for selection, the EAS score must be ≥16. See Section 17.5, Appendix E.
- The "Rule of Nines" is used to estimate the maximum percentage of AD-affected BSA in each area: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%] and genitals [1%]. The number of palms of AD-affected skin in a body part can be used to determine the extent (%) of AD involvement in that body part. Regardless of the age of the subject, the area of the subject's entire palm (five fingers adducted together) is about 1% of the subject's

BSA. The number of palms in different body parts is assessed to calculate the percentage of BSA affected by AD. It should be noted that in order to be eligible for selection, the percentage of AD-affected BSA must be ≥10. See Section 17.6, Appendix F.

- AD score (SCORAD): It is a clinical tool used to assess the severity of AD (extent/severity) and subjective signs/symptoms (e.g., itch/sleeplessness). The degree of lesions is scored using the "rule of nines" method. The severity is determined by grading the severity of the 6 signs (erythema, edema, oozing/crusting, excoriation, lichenification, and skin dryness) on a 0-3 subscale. The assessment of each sign is scored on the most representative skin lesions. See Section 17.7, Appendix G.

Note: in order to facilitate the assessment of dryness and scales, the use of emollients should be avoided within 4 hours before the assessment of AD.

6.2.1. Screening Period (D-28~D-1)

After the patient signs the ICF, the patient's eligibility for study enrollment will be assessed at the first screening visit within 28 days before the baseline visit. During this period, patient information to be collected or assessment to be performed is as follows:

- Demographic characteristics;
- Medical history;
- Review of inclusion and exclusion criteria;
- Height and weight;
- Hepatitis and HIV screening: Hepatitis screening includes HBsAg, HBcAb, HBV-DNA and hepatitis C antibodies, HCV-RNA;
- Physical examination: A complete physical examination is required, including general appearance, skin, eyes/ears/nose/throat, head and neck, cardiovascular system, respiratory system, abdomen, limbs, lymph nodes, musculoskeletal and nervous systems. Unless it is necessary to assess the status of AD involvement, there is no need to perform rectal or genital examinations;
- Vital signs (VS): Including body temperature, respiratory rate, blood pressure (BP), and heart rate (HR). The subject should sit and rest for at least 3 minutes before VS assessment;
- 12-lead ECG;
- Chest X-ray examination;
- Eye examination: At each visit, the investigator must assess whether the subject has any eye discomfort, such as redness, itching, photophobia and abnormal discharge, as well as related signs/symptoms, such as conjunctival hyperemia and exudate. If these discomforts are considered to be related to conjunctivitis or keratitis or any uncertain diagnosis, an ophthalmologist should conduct further assessment and give

appropriate treatment.

- Safety laboratory tests: Including hematology, blood biochemistry and urinalysis. See Table 9.1 for details;
- Blood pregnancy test: Only for FCBP;
- FSH test: Only for menopausal female subjects; subjects who can provide FSH test results before screening do not need to repeat the test;
- Investigator's efficacy assessments;
- Patient reported outcomes (including DLQI and POEM): To be assessed once a week during study period. The investigator will dispense the subject diary at each visit and collect DLQI and POEM data of that day, and the data among two visits will be assessed by the subjects themselves and recorded in the subject diary. Old diaries dispensed last time will be collected at the next visit and the new ones will be dispensed;
- PP-NRS score: The subject should record the PP-NRS score of the maximum pruritus intensity in the past 24 hours every day within 7 days before the baseline visit (*in these 7 days, the scores of at least 4 days are required for the calculation of the baseline average score. If the patient's reporting days are less than 4 days in the 7 days before the planned date of randomization, randomization should be postponed until the requirements are met, but it is not allowed to exceed the maximum screening period of 28 days*);
- Use of mild emollients: Emollients should be used at least 7 days before the baseline visit, at least twice a day; if the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period;
- Pre-treatment adverse event (PTAE);
- Prior and concomitant medication/treatment.

6.2.2. Stage 1 Treatment Period

6.2.2.1. D1: Baseline and Study Drug Administration

The study staff must review all screening laboratory test results before baseline (D1) to confirm that the subjects are eligible for selection.

D1 pre-dose visit

Subjects who are qualified during the screening visit must return to the study site within 28 days after the screening.

Before D1 administration, the subject's information to be collected or assessment to be performed is as follows:

- Confirmation of ICF signing;

- Review of inclusion and exclusion criteria;
- Weight;
- VS;
- 12-lead ECG;
- Eye examination;
- Safety laboratory tests: Test results within 7 days before baseline are acceptable, and there is no need to repeat the test;
- Urine pregnancy test: Only for FCBP;
- PK blood sample collection;
- PD/ADA blood sample collection;
- Investigator's efficacy assessments;
- Patient reported outcomes;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- Randomization: Subjects who are eligible for enrollment after D1 pre-administration screening will be randomized in a 2:1 ratio to the CBP-201 group or placebo group for treatment;
- PTAEs;
- Concomitant medication/treatment.

D1 post-dose visit

After D1 administration, the subject's information to be collected or assessment/procedure to be performed is as follows:

- SC administration of study drug;
- VS: VS will be recorded q1h × 2h (±10 min) after administration (T0). Subjects should rest in a sitting position for at least 3 min before VS assessment;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions;
- AEs;
- Concomitant medication/treatment.

6.2.2.2. D15/W2 Visit

Subjects will return to the study site at W2±3d to receive study drug injections and the following assessments:

- VS: VS will be recorded before and q1h × 2h (±10 min) after administration. Subjects should rest in a sitting position for at least 3 min before VS assessment;
- Eye examination;
- Safety laboratory tests;
- PK blood sample collection;

- PD/ADA blood sample collection;
- Investigator's efficacy assessments;
- Patient reported outcomes;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- SC administration of study drug;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed before administration, and the new injection site should be assessed before the subject leaves the study site;
- AEs;
- Concomitant medication/treatment.

6.2.2.3. Q2W Visits During D29/W4~D99/W14

Subjects will return to the study site at W4±3d and every 2 weeks during the treatment period thereafter until W14±3d to receive study drug injections and complete the corresponding study procedures according to the Study Flow Chart.

The subject's information to be collected or assessment/procedure to be performed during W4~W14 is as follows:

- Weight: Measured at W4, W8 and W12;
- VS: VS will be recorded before and q1h × 2h (±10 min) after administration at W4, and before and 30 min (±10 min) after administration from W6 to W14. Subjects should rest in a sitting position for at least 3 min before VS assessment;
- Eye examination: This must be performed at each visit during W4~W14;
- Safety laboratory tests: Performed at W4 and W8;
- Urine pregnancy test: Only for FCBP, performed at W4, W8 and W12;
- PK blood sample collection: Performed at W4, W8 and W12;
- PD/ADA blood sample collection: Performed at W4, W8 and W12; note: blood samples will not be collected for PD parameter—peripheral blood eosinophils at W12;
- Investigator's efficacy assessments: Performed at W4, W8 and W12;
- Patient reported outcomes: Performed at each visit;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- SC administration of study drug: During W4~W14, Q2W;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed before administration, and the new injection site should be assessed before the subject leaves the study site;

- AEs;
- Concomitant medication/treatment.

6.2.2.4. D113/W16 Pre-Dose Visit

Subjects will return to the study site at W16±3d to receive the following assessments:

- Weight;
- Physical examination;
- VS: VS will be recorded before administration. Subjects should rest in a sitting position for at least 3 min before VS assessment.
- 12-lead ECG;
- Eye examination;
- Safety laboratory tests;
- Urine pregnancy test;
- PK blood sample collection;
- PD/ADA blood sample collection;
- Investigator's efficacy assessments;
- Patient reported outcomes;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- Randomization: Only subjects whose W16 pre-dose treatment assessment meets the response criteria will be randomized;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed before administration;
- AE;
- Concomitant medication/treatment.

6.2.3. Stage 2 Maintenance Treatment Period (W16~W52)

Before W16 administration, all subjects will be assessed for efficacy, and treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in EASI score (ie EASI-50). The first dose of Stage 2 will be administrated at W16. After that, subjects will return to the study site every 2 weeks to receive the study drug injections and complete the corresponding study procedures according to the Study Flow Chart.

6.2.3.1. D113/W16 Post-Dose Visit

Subjects will return to the study site at W16±3d to receive the study drug injections and the following assessments:

- VS: VS will be recorded q1h × 2h (±10 min) after administration;
- SC administration of study drug;

- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The new injection site should be assessed before the subject leaves the study site;
- AEs;
- Concomitant medication/treatment.

6.2.3.2. Q2W Visits During D127/W18~D365/W52

Subjects will return to the study site at W18±3d and every 2 weeks during the treatment period thereafter until W52±3d to receive study drug injections and complete the corresponding study procedures according to the Study Flow Chart.

The subject's information to be collected or assessment/procedure to be performed during W18~W52 is as follows

- Weight: During W20~W52, Q4W;
- Physical examination: Performed at W52;
- VS:
  - At W18 and W20, VS will be recorded before and q1h × 2h (±10 min) after administration;
  - From W22 to W50, VS will be recorded before and 30 min (±10 min) after administration;
  - Subjects should rest in a sitting position for at least 3 min before VS assessment;
- 12-lead ECG: Performed at W52;
- Eye examination: During W18~W52, this must be performed at each visit;
- Safety laboratory tests: Performed at W24, W32, W40 and W48;
- Urine pregnancy test: Only for FCBP, from W20 to W52, Q4W;
- PK blood sample collection: During W20~W52, Q8W;
- PD/ADA blood sample collection: During W20~W52, Q8W; note: blood samples will not be collected for PD parameter—peripheral blood eosinophils at W20, W28, W36, W44 or W52;
- Investigator's efficacy assessments: During W20~W52, Q4W;
- Patient reported outcomes: Performed at each visit during W20~W52;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- SC administration of study drug: During W18~W50, Q2W;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed before administration, and the new injection site should be assessed before the subject leaves the study site (only previous injection site is assessed at W52);
- AEs;
- Concomitant medication/treatment.

6.2.4. Follow-up Period (D393/W56, D421/W60)

After W52, subjects will not receive any study drug SC treatment, but return to the study site within the next 8 weeks to receive a follow-up visit and other study procedures.

At the follow-up visit, the subject's information to be collected or the assessment/procedure to be performed is as follows:

- Weight: Measured at W56 and W60;
- Physical examination: Performed at W60;
- VS: Monitored at W56 and W60;
- 12-lead ECG: Performed at W60;
- Eye examination: Performed at W56 and W60;
- Safety laboratory tests: Performed at W60;
- Urine pregnancy test: Only for FCBP, performed at W56 and W60;
- PK blood sample collection: Performed at W60;
- PD/ADA blood sample collection: Performed at W60;
- Investigator's efficacy assessments: Performed at W56 and W60;
- Patient reported outcomes: Performed at W56 and W60;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed at W56 and W60;
- AEs;
- Concomitant medication/treatment.

6.2.5. Early Termination (ET)

If the subject early terminates (ET) the study for any reason, the ET visit should be completed within 7 days after ET. If the treatment is early terminated, the 8-week follow-up visit is required.

At the ET visit, the subject's information to be collected or the assessment/procedure to be performed is as follows:

- Weight;
- Physical examination;
- VS;
- 12-lead ECG;
- Eye examination;
- Safety laboratory tests;
- Urine pregnancy test: Only for FCBP;
- PK blood sample collection;

- PD/ADA blood sample collection;
- Investigator's efficacy assessments;
- Patient reported outcomes;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- Use of mild emollients: At least twice a day;
- Assessment of injection site reactions: The previous injection site should be assessed;
- AEs;
- Concomitant medication/treatment.

6.2.6. Unscheduled Visits

During the study period, the investigator can decide whether to increase unscheduled visits based on clinical needs (e.g., AD deterioration, clinically significant laboratory test abnormalities, AEs, etc.). During the unscheduled visits, the corresponding examinations and AEs should be truthfully recorded.

At unscheduled visits, the subject's information to be collected or the assessment/procedure to be performed is as follows:

- Physical examination;
- VS;
- PP-NRS score: The PP-NRS score of the maximum pruritus intensity in the past 24 hours is recorded every day;
- Assessment of injection site reactions: The previous injection site should be assessed;
- AEs;
- Concomitant medication/treatment.

6.3. Randomization and Blinding

6.3.1. Randomization

In the course of this study, subjects will be randomized twice:

1) After subjects complete the screening period and meet the inclusion criteria after D1 pre-dose assessment, they can be randomized to Group A (CBP-201 300 mg Q2W) or Group B (placebo Q2W) in a 2:1 ratio before D1 administration;
2) Subjects who are assessed to have met the response criteria before W16 administration will be randomized to Group C (CBP-201 300 mg Q2W) or Group D (CBP-201 300 mg Q4W) in a ratio of 1:1.

Subjects will be stratified and randomized according to their baseline disease severity (moderate [IGA=3] and severe [IGA=4]) to avoid bias and increase the likelihood of keeping

known and unknown subject attributes (e.g., demographics and other baseline characteristics) or other variables balanced between treatment groups and increase the validity of statistical comparisons between treatment groups.

The placebo control will be used to determine the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active drug treatment, and to minimize the bias of subjects and investigators.

6.3.2. Blinding

Double-blind treatment will be used to reduce the potential bias of subjects and investigators during data collection and assessment of clinical endpoints.

During the study period, double-blind treatment group assignment will be adopted. Subjects, study site staff, the sponsor, and personnel designated by the sponsor directly involved in the conduct and/or monitoring of this study shall not be aware of the status of treatment group assignment. In the PK part of the study, blood will be collected from all subjects participating in the study (regardless of receiving CBP-201 or placebo treatment) at a designated time point and sent to the bioanalysis laboratory for subsequent processing. Since the treatment group assigned to any subject is not unblinded to any of the study site staff, the blindness can be maintained during PK sampling.

At each stage of the study, unblinding of subject grouping information of corresponding stages shall not be performed until all subjects have completed scheduled visits of corresponding stages and the data cleaning, blind data reviewing and locking is completed. During the study period, unblinding can only be performed when the investigator believes that it is necessary to unblind in order to treat the AE or other emergency medical events that have occurred in the subject. If possible, the investigator should contact the sponsor before unblinding and after taking any measures. Whenever the treatment sequence is unblinded early, the reason for unblinding, the date, time and implementer of unblinding must be recorded.

After the 255 subjects enrolled based on the V2.1 and prior versions of the protocol complete the stage 1 study, the study data of the 255 subjects at stage 1 will be unblinded and analyzed, but the investigator and other staff related to the study site will still be blinded to the subject grouping information. See unblinding limitations and blinding maintenance charter of this project for details.

7. Subject Selection and Withdrawal

7.1. Inclusion Criteria

Patients must meet all of the following criteria to be enrolled into this study:

1) 12≤ age ≤75 years at the screening visit, male or female; *note: the adolescent subjects aged <18 years should have body weight ≥40 kg.*

2) Diagnosed with atopic dermatitis (according to the American Academy of Dermatology's Guidelines of care for the management of atopic dermatitis, 2014[1]) at the time of screening, and:

   a) The subject has been suffering from the disease for more than 1 year at the time of screening, and according to the judgment of the investigator, the subject has had poor response to topical drugs such as corticosteroids, phosphodiesterase-4 (PDE-4) inhibitors or calcineurin inhibitors (TCI), or it is not medically suitable for the subject to receive topical drug treatment (e.g., there are important side effects or safety risks);

   Note: Poor response is defined as any of the following conditions:

      i. The patient has not achieved and maintained response or reached a low disease activity state (equivalent to IGA 0=asymptomatic to 2=mild) despite regular use of topical therapy during the 1 year before baseline;

      ii. The patient has received systemic treatment for AD despite regular use of topical therapy during the 1 year before baseline.

   b) At the screening and baseline visit, Investigator's Global Assessment (IGA) score≥3 (according to the validated Investigator Global Assessment for Atopic Dermatitis [vIGA-AD™] scale, see Section 17.4 Appendix D), Eczema Area and Severity Index (EASI) score ≥16 (see Section 17.5, Appendix E), and ≥10% body surface area (BSA) of AD involvement (see Section 17.6, Appendix F);

   c) The average score of the maximum pruritus intensity in the Peak Pruritus Numerical Rating Scale (PP-NRS)≥4(see Section 17.1, Appendix A).

Note: The baseline average maximum pruritus PP-NRS intensity score will be calculated based on the average value of the maximum pruritus intensity PP-NRS score [daily score range 0-10] every day within 7 days before randomization. In these 7 days, the scores of at least 4 days are required for the calculation of the baseline average score. If the patient's reporting days are less than 4 days in the 7 days before the planned date of randomization, randomization should be postponed until the requirements are met, but it is not allowed to exceed the maximum screening period of 28 days.

3) Be able to and willing to use a stable dose of a mild emollient at the AD involvement area at least twice a day starting from at least 7 days before baseline and continue to use it during the study period (see Section 8.1.1.2 Emollients).

4) Female subjects of childbearing potential (FCBP) and male subjects who have not undergone vasectomy must take highly effective contraceptive measures during the entire study period, including the 8-week follow-up period after discontinuation of study drug. *Postmenopausal women (determined by testing follicle stimulating hormone [FSH]) and women with a record of surgical sterilization (i.e., tubal ligation or hysterectomy or bilateral oophorectomy) before the screening visit can be considered infertile.*

Highly effective contraceptive measures include:

i. Abstinence (acceptable only if it is part of the subject's routine lifestyle);

ii. Hormones (oral, patch, ring, injection, implant) combined with male condoms. This measure must be used at least 30 days before the first study drug administration. Otherwise, another acceptable method of contraception must be used;

iii. Intrauterine device (IUD) combined with male condoms;

iv. Exceptions are: a) women who have had amenorrhea for at least 12 consecutive months without using drugs known to cause amenorrhea, and have a recorded FSH level greater than 40 mIU/mL or in the postmenopausal range; or b) surgical sterilization (e.g., hysterectomy, bilateral oophorectomy).

5) Subjects and/or their guardians have the ability to learn the study requirements and process, and voluntarily take part in the clinical trial and sign an informed consent form (ICF); note: for subjects ≥18 years: subjects voluntarily agree to take part in the study by themselves and sign ICF; for subjects aged 12-17 years, subjects and their guardians voluntarily agree to take part in the study, the guardians sign the ICF, and the subjects sign the informed assent form for minors by themselves.

6) Subjects and/or their guardians are willing and able to comply with study visits and related procedures.

7.2. Exclusion Criteria

Patients who meet any of the following criteria cannot participate in this study:

1) Patients who have received any of the following treatments:
   a) Treatment with dupilumab or any anti-IL-4Rα or IL-13 antibody treatment;
   b) Topical drugs for treatment of AD or have the potential to affect the assessment of AD, including but not limited to corticosteroids, PDE-4 inhibitors, Janus kinase (JAK) inhibitors, aromatic hydrocarbon receptor agonists, tacrolimus or pimecrolimus, or traditional Chinese medicine (TCM) or herbal medicine, etc. within 2 weeks before baseline;
   c) Have undergone bleaching baths ≥ twice within 2 weeks before baseline;
   d) Have begun to use prescription emollients or emollients containing additives (e.g., ceramide, hyaluronic acid, urea, or filaggrin breakdown products) to treat AD from

the screening period (if the subject has started using this kind of emollient before the screening visit, they can continue to use it at a stable dose; if the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period);

e) Treatment with systemic corticosteroids or other immunosuppressive/immunomodulating substances (e.g., cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, or oral JAK inhibitors) due to AD or other diseases within 4 weeks before baseline (*except for corticosteroid inhalers and nasal sprays*);

f) Treatment with systemic TCM or herbal treatment within 4 weeks before baseline (note: except for those for the treatment of diseases other than AD, which are necessary and will neither increase the risks of the subjects nor affect the assessment of the study in accordance with the medical judgements of the investigator and/or specialist physician);

g) Treatment with phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), sunbed or any other light emitting device (LED) therapy within 4 weeks before baseline;

h) Have used any investigational drug/treatment within 4 weeks before baseline or 5 drug half-lives, whichever is longer;

i) Treatment with other biological agents (e.g., omalizumab) within 3 months before baseline or 5 drug half-lives (if known), whichever is longer;

j) Have been vaccinated with live (attenuated) vaccine within 8 weeks before baseline;

k) Treatment with cell depletion agents (e.g., rituximab) within 6 months before baseline;

l) Treatment with allergen specific immunotherapy (SIT) within 6 months before baseline (except those who were already on stable-dose therapy before baseline).

2) Patients who meet any of the following:

a) History of hypersensitivity to L-histidine, trehalose or Tween 80;

b) Other skin complications in addition to AD that may interfere with the study assessments;

c) Any history of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC);

d) History of malignant tumor within 5 years before screening, except for cervical carcinoma in situ or non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma;

e) Active tuberculosis (TB) at the screening visit, latent tuberculosis or a history of non-tuberculous Mycobacterium infection;

Note:

- Unless there is a clear specialist record proving that the patient has received adequate treatment and is currently able to start receiving biological treatment (based on the medical judgment of the investigator and/or infectious disease specialist);
- If necessary, T-spot test may be used for auxiliary diagnosis of suspected tuberculosis patients;

f) Positive for hepatitis B surface antigen (HBsAg), or positive for hepatitis B core antibody (HBcAb) and HBV-DNA, or positive for hepatitis C antibody and HCV RNA polymerase chain reaction, or serologically positive for human immunodeficiency virus (HIV) at the screening visit;

g) Any of the following laboratory test abnormalities at the screening visit:
   i. Aspartate aminotransferase or alanine aminotransferase > 2 times the upper limit of normal (ULN), or total bilirubin > 1.5×ULN;
   ii. Serum creatinine > 1.2×ULN;
   iii. Hemoglobin < 8.5 g/dl (85.0 g/L) in male patients and < 8.0 g/dl (80.0 g/L) in female patients;
   iv. White blood cell count $<3.0\times10^9$/L or $\geq14\times10^9$/L;
   v. Platelet count $<100\times10^9$/L.

Note: if the subjects have the above laboratory test abnormalities at screening, after being assessed as necessary by the investigator, they are allowed to receive a retest at another day within 28 days of the screening period, and those qualified for the retest are permitted to be enrolled (*it is forbidden to conduct drug intervention for those laboratory test abnormalities before retest*).

h) Planning to undergo major surgical operations during the study period;

i) Used systemic treatment with antibiotics, antiviral drugs, antiparasitic drugs, antigenic drugs, or antifungal drugs due to infection within 4 weeks before the baseline visit, or suffered from superficial skin infection (e.g., impetigo) within 2 weeks before baseline (after the infection subsides, the subjects can be rescreened);

j) History of parasite infection (e.g., helminth) within 6 months before baseline;

k) According to the investigator's judgment, there is a known or suspected history of immunosuppression within 6 months before baseline, including a history of invasive opportunistic infections, such as aspergillosis, coccidiosis, histoplasmosis, HIV, listeriosis, Pneumocystis or tuberculosis, even if the infection has subsided, or there is an abnormally frequently recurrent or persistent infection;

l) History of alcohol or drug abuse within 2 years before the screening visit;

m) Any other medical or psychological condition (including clinically significant laboratory test abnormalities, ECG parameters, etc.) at the screening visit, which, as judged by the investigator, may indicate new and/or insufficiently understood diseases, may put the patient at an unreasonable risk due to his/her participation in the clinical trial, may lead to unreliable results of the patient's participation, or may

interfere with the study assessments. The specific reasons for patients excluded due to this criterion will be indicated in the study documents (medical records, CRF, etc.).

3) Pregnant or lactating women, or subjects with pregnancy or lactation plans during the study period.

7.3. Early Withdrawal

During the trial, subjects have the right to withdraw from the study at any time for any reason. The investigator can also require subjects to withdraw from the study for safety, subject compliance and other reasons. Subjects who withdraw from this study will not be discriminated or retaliated upon, and their medical treatment and rights will not be affected.

For subjects who early withdraw from the study, while respecting the personal wishes of the subjects, the investigator should make every effort to determine the reason why the subjects early withdraw from the study and make corresponding records.

The reasons for the subject's withdrawal from the study may include but not be limited to the following:

1) The subject withdraws the informed consent.
2) The subject is lost to follow-up.
3) Complications and medical conditions that require termination of the study treatment, based on the judgment of the investigator and the sponsor.
4) Protocol deviations, based on the judgment of the investigator and the sponsor.
5) The investigator believes that the subject has an intolerable AE or SAE, is not suitable for continuing the study treatment, and needs to withdraw from the study.
6) The investigator judges that withdrawing from the study is to protect the interests of the subject.
7) Pregnancy.
8) The investigator believes that the subject has poor compliance, which may make the subject’s study results unevaluable.
9) The treatment is unblinded.
10) The sponsor requires so.
11) Other situations where the investigator believes that the subject has to withdraw from the trial.
12) The study is terminated.

Subjects who early withdraw from the study during the study treatment period (including Stage 1 treatment period and Stage 2 maintenance treatment period) should complete the early

termination visit as far as possible within 7 days of ET according to the protocol, and complete the 8-week safety follow-up as far as possible. The investigator or study-related personnel with corresponding qualifications should contact the subjects as much as possible, try their best to collect the assessment content that needs to be completed at the corresponding visits, and make records, including the date of the last study drug administration, the date of withdrawal from the study, and the reason for withdrawal.

For subjects who withdraw from the study, regardless of the reason, their eCRF should be retained. The biological samples that have been obtained should be retained, processed and tested.

7.4. Study Termination

The sponsor has the right to terminate this study at any time, and the sponsor and the investigator have the right to close the study site at any time. Of course, this can only be implemented after mutual negotiation. When terminating the study early, the investigator should promptly notify the subject and complete the follow-up visit as planned in the protocol. If there is an AE, the subject should be followed up until the AE disappears or stabilizes.

When the sponsor early terminates the study, the sponsor should immediately inform the investigator, clinical trial institution, and drug regulatory authority, and explain the reason for the termination of the study.

If the investigator early terminates the study without consulting the sponsor, the investigator should immediately report to the clinical trial institution, the sponsor and the EC, and provide a detailed written explanation; if the sponsor early terminates the study, the investigator should immediately report to the clinical trial institution and the EC, and provide a detailed written explanation.

When the EC terminates the study, the investigator should immediately report to the clinical trial institution and the sponsor, and provide a detailed written explanation.

The reasons for early termination of the study or closure of a study site may include but not be limited to the following:

- The sponsor requests termination under the premise of fully protecting the rights and interests and safety of subjects (e.g., funding reasons, management reasons, etc.).
- A significant deviation or human error is found during the implementation of the trial, which seriously affects the quality of the trial and makes it difficult to achieve the objectives of the trial.
- New information leads to unfavorable risk/benefit judgments of the study drug, such as:
  - The study drug lacks efficacy, whether in this study or other studies; or
  - Significant, previously unknown adverse drug reactions or unexpected, high-severity/incidence known adverse drug reactions occur; or

  - Other adverse safety findings, including clinical examination and non-clinical manifestations.
- Due to the difficulty in patient enrollment, making it unlikely to complete the study within an acceptable time frame.
- The study is discontinued or terminated as required by the EC.
- The study is discontinued or terminated as required by the competent health or regulatory authority.

8. Study Treatment

8.1. Study Treatment Drugs

8.1.1. Basic Information of Study Treatment Drugs

8.1.1.1. Investigational Drug/Placebo

Table 8.1 Detailed Information of Investigational Drug/Placebo

Study drug	Investigational drug	Placebo
Drug name	CBP-201	/
Dosage form	Injection	
Composition	CBP-201 is prepared from a solution containing inactive excipients (including NaCl, trehalose, Tween 80 and L-histidine) at a concentration of 150 mg/ml.	Contains the same excipients, but does not contain CBP-201 API.
Storage	CBP-201 preparation and the corresponding placebo solution should be stored at 2-8 ° C.	
Method of administration	Subcutaneous injection (SC)	
Dosing regimen	Detailed in Section 6.1.	

All study treatment drug bottles are blinded and can only be identified by the drug bottle number on the bottle label.

8.1.1.2. Emollients (Background Treatment)

From at least 7 days before baseline to the end of the study, subjects will be required to apply a mild emollient to the AD-affected area at least twice a day as background treatment, but should avoid using emollients within 4 hours before AD assessment at each visit. During the screening period or the study period, subjects cannot start using prescription emollients or emollients containing additives. However, if subjects have already started using these emollients before the screening visit, they can use them at a stable dose throughout the study period. If the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to the emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period.

8.1.2. Dose Selection

The preliminary safety of CBP-201 has been established in a Phase I SAD study in healthy subjects (subjects receiving doses ranging from 75 mg to 600 mg) and a MAD study in AD subjects (subjects receiving 75 mg, 150 mg, or 300 mg QW for 4 times), and it was seen that 300 mg QW showed more significant efficacy. Based on the above studies, the dosage regimen (CBP-201 300 mg Q2W or Q4W) selected in this study may be well tolerated.

8.1.3. Drug Package and Label

The sponsor and the contract research organization (CRO) will design labels for all study drugs and perform drug packaging and labeling in accordance with the Good Clinical Practice (GCP)

and applicable national regulations. The label content includes information such as protocol number, drug number, drug name, dosage form, strength, batch number, production date, expiration date, instructions for use, package, storage, appropriate warnings and name of the sponsor, and "for clinical research use only" should be indicated.

From the perspective of the blinding method of the clinical trial, the inner and outer packaging of the study drug will be kept consistent with that of the placebo.

8.1.4. Drug Distribution, Recording and Recovery

The study drugs used in this trial (investigational drug CBP-201 and placebo) will be provided by the sponsor free of charge and distributed to each study site as planned. Each clinical study site will appoint a person to be responsible for the reception, custody, distribution, recovery and corresponding recording of study drugs.

The study drug management of each clinical study site should meet the following requirements:

1) A designated person (e.g., a pharmacist) will receive the study drugs and materials provided by the sponsor and keep a record;
2) A designated person is responsible for the reasonable and safe storage of study drugs, and should ensure that the storage conditions of study drugs meet the requirements;
3) The distribution and use of study drugs and materials need to be fully recorded;
4) Study drugs can only be prescribed by the investigator or a study doctor authorized by the investigator;
5) Study drugs can only be distributed to qualified subjects in accordance with the trial protocol, and non-study subjects are not allowed to use study drugs;
6) The investigator should keep unused medicines and packaging, and outer packaging of used medicines for inspection by the clinical research associate (CRA);
7) After the drugs are counted during the visit, detailed records should be kept on medication errors, overdose, drug loss and other situations;
8) After being counted by the CRA, the remaining unused drugs and the outer packaging of used drugs will be recovered by the sponsor.

The investigator or his designated personnel must agree not to provide study drugs to any subjects who have not been enrolled into this study, or any physician or scientist who is not authorized for this study.

At the end of the trial, the study drug delivery records must be consistent with the used and destroyed/returned quantities. Any discrepancies need to be recorded and the reasons for the discrepancies should be specified.

8.2. Concomitant Medications/Treatments

8.2.1. Prohibited Drugs/Treatments

The following drugs/treatments are prohibited during the study period. If any of the following treatment is started after the first dose of study drug on D1, the study treatment must be early terminated:

- Dupilumab or any anti-IL-4Rα or IL-13 antibodies;
- Topical PDE-4 inhibitors or JAK inhibitors;
- Systemic treatment with corticosteroids or other immunosuppressive and/or immunomodulatory agents such as cyclosporine, mycophenolate mofetil, azathioprine, methotrexate or oral JAK inhibitors;
- Cell depletion agents (e.g., Rituximab) or other biological agents;
- Other investigational drugs (non CBP-201) or treatments.

The following treatments are also prohibited during the study period:

- Initiation of SIT or dose up-regulation;
- (Attenuated) live vaccine;
- TCS or TCI;
- Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies;
- Bleaching baths more than 2 times a week;
- Any drug (except mild emollients) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity.

8.2.2. Permitted Drugs/Treatments

a. AD recurrence and rescue therapy

AD is a chronic recurrent skin disease characterized by periodic aggravation or gradual deterioration of symptoms. If medically necessary (i.e. in order to control intolerable AD symptoms), the investigator can provide patients with rescue therapy for AD by using drugs or treatment regimens that were originally prohibited at their own discretion. According to the investigator's judgment, AD aggravation or deterioration of symptoms which requires drugs or treatments originally prohibited by the protocol for rescue therapy will be defined as “AD recurrence” event, and the onset and duration of these events will be recorded as AE according to the site of attack.

Note: The investigator should limit the first-step rescue therapy to topical drugs (TCS or TCI) as far as possible. Only patients who do not respond adequately after at least 7 days of topical medication can be upgraded to systemic medication or other treatments. If a subject receives systemic corticosteroid or non-steroid systemic immunosuppressive/immunomodulatory rescue therapy, the study drug administration will be stopped immediately.

b. Other drugs that are permitted may include:

- Emollients (as the background treatment of this study, at least 7 days before baseline, all subjects need to use mild emollients at least twice a day, and continue to use them throughout the study period. During the screening period or the study period, subjects cannot start using prescription emollients or emollients containing additives. However, if a subject has already started using these emollients before the screening visit, he/she can continue using them at a stable dose throughout the study period. If the subject is intolerable to the emollients provided uniformly by the sponsor during the screening period, he/she can change to the emollient of this kind used previously, but it must be used at a stable dose for at least 7 days before baseline and during the study period.);
- Basic skin care (cleansing and bathing);
- Oral antihistamines (maintain a stable dose within 7 days before baseline and during the study period);
- Drugs for the treatment of chronic diseases (e.g., hypertension, diabetes, etc.);
- Local or systemic anti-infective drugs (as required by the condition).

Before any rescue therapy, the investigator should make every effort to assess the efficacy and safety (e.g., disease severity score, safety laboratory tests). If necessary, unscheduled visits can be conducted.

8.3. Treatment Compliance

As all study treatment drugs (CBP-201 and placebo) are administered by study personnel, the subjects therefore are not required to follow procedures.

9. Study Procedures and Endpoints

9.1. Informed Consent

The investigator or designated study staff will explain to the subjects and/or their guardians the nature of the study and its risks and benefits. Before performing any study-related procedures, subjects and/or their guardians must voluntarily sign an ethically approved ICF to provide written informed consent.

9.2. Demographics and Other Baseline Characteristics

9.2.1. Demographics/Baseline Characteristics

Demographic data of subjects will be recorded, including age and gender.

9.2.2. Medical History and History of Surgery

The complete medical history and surgical history will specifically include the history of AD and acute, chronic or infectious diseases within 1 year before screening, the history of surgery or tumor, and any reported diseases that affect major body systems. The investigator will assess the clinical significance of the subject's medical history. The medical history should be

reviewed and updated at the baseline visit (D1 pre-dose).

9.2.3. Medication/Treatment History

All drugs (prescription drugs and over-the-counter drugs, herbal/natural health products or study drugs) taken by the subjects within 30 days before the screening visit will be recorded in the source file as a medication history and recorded in the database of the prior and concomitant medications. Similarly, any treatment received by the subject will also be recorded in the source file as a treatment history.

Any new medications/treatments during the study period will be recorded in the source file and recorded in the appropriate CRF.

9.2.4. Height and Weight

Height: Measured during the screening period only.

Weight: Measured once each during the screening period and on D1, and measured once every 4 weeks during W4~W60. If the subject early terminates the study, it is also necessary to measure the weight at the ET visit.

9.2.5. Vital Signs

VS should be monitored at each visit. After the subject has a sitting rest for at least 3 minutes, the following vital signs will be measured: blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min), and body temperature. On D1 and at W2, W4, W16, W18, and W20, VS should be monitored every hour (±10 min) pre-dose and during the 2-hour monitoring period post-dose; from W6 to W14 and from W22 to W50, VS must be monitored pre-dose and 30 min (±10 min) post-dose.

If the investigator believes that the fluctuation of vital signs is clinically significant, it will be considered an AE.

9.2.6. Physical Examination

A complete physical examination (PE) is required at screening, W16, W52, EOS/ET and unscheduled visits. The items included are as follows: general appearance, skin, eyes/ears/nose/throat, head and neck, cardiovascular system, respiratory system, abdomen, limbs, lymph nodes, musculoskeletal and nervous systems. Unless it is necessary to assess the status of AD involvement, there is no need to perform rectal or genital examinations. Priority PE can be performed at visits where PE are not scheduled. Attention should be paid to the assessment of AD involvement areas.

9.3. AD Assessments

The assessment of the severity and impact of AD will be divided into two parts: the investigator's efficacy assessments and the patient reported outcomes. See Section 6.2 for details.

9.4. Other Safety Assessments

9.4.1. Safety Laboratory Tests

The hematology stipulated in the protocol will be performed in the central laboratory, and blood biochemistry and urinalysis performed in the local laboratory (if they can not be performed in the local laboratory, the samples will be sent out to the central laboratory for detection). Blood samples will be collected, processed and transported in accordance with the instructions of the central laboratory. If the laboratory results are abnormal or clinical symptoms appear, the investigator can collect additional samples for retesting as appropriate to ensure safety. The required laboratory assessments are listed in the table below.

Table 9.1 Safety Laboratory Tests

Hematology	Blood biochemistry	Urinalysis
White blood cell count	Sodium	Bilirubin
Hemoglobin	Potassium	Red blood cells
Hematocrit	Calcium	White blood cells
Red blood cell count	Chlorine	Glucose
Platelet count	Serum urea/urea nitrogen	Ketone
Neutrophil percentage	Creatinine	Nitrite
Lymphocyte percentage	Glucose	pH
Monocyte percentage	Total protein	Protein
Basophil percentage	Albumin	Urine specific gravity
Eosinophil percentage	Total bilirubin	Urobilinogen
Absolute neutrophil count	Alanine aminotransferase	Microscopic examination (if necessary)
Absolute lymphocyte count	Aspartate aminotransferase	
Absolute monocyte count	γ-glutamyltransferase	
Absolute eosinophil count	Alkaline phosphatase	
Absolute basophil count	Lactate dehydrogenase	
	Creatine phosphokinase	
	Total cholesterol	
	Low-density lipoprotein	
	High-density lipoprotein	

The investigator is responsible for reviewing and signing all laboratory tests reports, and for recording the appropriate safety monitoring of the study subjects. The investigator should sign and date each laboratory report while reviewing it, and should indicate the clinical significance of each abnormality/marked value by indicating “NCS” (not clinically significant) or “CS” (clinically significant). Annotations indicating that a value has clinical significance should also include a short description of the underlying disease or condition associated with the value, such as “CS/mild anemia”. Generally, abnormal laboratory values which are clinically significant judged by the investigator are expected to be associated with items recorded in the medical history or AEs. The investigator can use the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 [32] to assist in judging the severity and clinical significance.

9.4.2. 12-lead ECG (ECG)

The 12-lead ECG should be performed after the subject rests for at least 5 minutes in the lying/supine position. ECG variables include ventricular heart rate and PR, QRS, QT and QTcF intervals (formula: $QTcF=QT/RR^{0.33}$). The ECG will be signed and dated by a medically qualified person to confirm that the ECG has been reviewed and to confirm whether an ECG abnormality (if any) is clinically significant.

9.4.3. PK and PD Sampling

PK sampling will be implemented according to the Study Flow Chart. About 4 ml of whole blood will be collected each time, and plasma will be separated to analyze the blood concentration of CBP-201. The PK characteristics of steady-state trough concentrations of individuals and each group of subjects at each treatment time point will be calculated.

PD sampling will be implemented according to the Study Flow Chart. About 5 ml of whole blood will be collected each time to summarize the changes in serum IL-4, IL-13, IgE and TARC and peripheral blood eosinophil count from baseline.

9.4.4. ADA Sampling

ADA sampling will be implemented according to the Study Flow Chart. About 5 ml of whole blood will be collected each time for ADA testing. All ADA-positive samples will be further tested to determine the presence of anti-CBP-201 NAb.

9.4.5. Sample Processing

Please refer to the CBP-201-CN002 laboratory manual for a detailed description of the processing and labeling requirements after the collection of PK/PD/ADA samples.

9.5. Study Endpoints

9.5.1. Efficacy Endpoints

➢ **Primary endpoint**

The proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W16.

➢ **Key secondary endpoints**

- The proportion of subjects achieving EASI-75 at W16;
- The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 4 points from baseline at W16;
- The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 3 points from baseline at W16;
- Change and percentage change in the weekly average PP-NRS from baseline at W16;
- The proportion of subjects achieving EASI-90 at W16;

➢ **Other secondary endpoints**

- Change and percentage change in the EASI score from baseline at W16;
- The proportion of subjects achieving EASI-50 at W16;
- Percentage change in the BSA of AD involvement from baseline at W16;
- Percentage change in the SCORAD score from baseline at W16;
- Change in DLQI from baseline at W16;
- Change in POEM from baseline at W16;
- Percentage change in the weekly average PP-NRS from baseline at W2.

➢ **Other efficacy endpoints**

- The proportion of subjects whose IGA score is decreased by ≥ 2 points from baseline at W16;
- The proportion of subjects achieving EASI-100 at W16;
- The number of AD recurrences and number of days from baseline to W16;
- Change in efficacy parameters (e.g., IGA, EASI, BSA, SCORAD, POEM and DLQI) from baseline to W16;
- Change in weekly average PP-NRS from baseline at W16;
- The proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W52;
- The percentage decrease in the overall EASI score between W16 and W52;
- The proportion of subjects achieving EASI-50 at W52;
- The proportion of subjects achieving EASI-75 at W52;
- The proportion of subjects achieving EASI-90 at W52;
- The proportion of subjects achieving EASI-100 at W52;
- Change in weekly average PP-NRS compared with baseline from W16 to W52;
- Change in POEM compared with baseline from W16 to W52;
- The proportion of subjects whose IGA score is decreased by ≥2 points from baseline at W52;
- Percentage change in the AD-affected BSA compared with baseline from W16 to W52;
- Change in SCORAD compared with baseline from W16 to W52;

- The proportion of subjects whose weekly average PP-NRS is decreased by ≥3 points from baseline at W52;
- The proportion of subjects whose weekly average PP-NRS is decreased by ≥4 points from baseline at W52;
- Change in PDLQI compared with baseline from W16 to W52;
- The number of subjects with AD recurrence from baseline to W8;
- The number of subjects with AD recurrence from W8 to W16;
- The number of subjects with AD recurrence from W16 to W52;
- The number of AD recurrences and number of days from W16 to W52.

Note: EASI 50: EASI score is decreased by ≥50% from baseline; EASI 75: EASI score is decreased by ≥75% from baseline; EASI 90: EASI score is decreased by ≥90% from baseline; EASI-100: EASI score is decreased by 100% from baseline; PP-NRS: Peak Pruritus Numerical Rating Scale; AD recurrence: According to the investigator's judgment, AD aggravation or deterioration of symptoms which requires drugs or treatments originally prohibited by the protocol for rescue therapy will be defined as "AD recurrence" event; POEM: Patient Oriented Eczema Measure; SCORAD: Scoring Atopic Dermatitis Index; DLQI: Dermatology Life Quality Index.

9.5.2. Safety Endpoints

Safety assessments are based on the following indicators:

- Incidence and severity of AE, AESI and SAE;
- Abnormal changes in vital signs, physical examination, and the injection site;
- Abnormal changes in laboratory tests, ECG parameters, etc.;
- Percentage of subjects positive for ADA.

9.5.3. PK Endpoints

To analyze the blood concentration of CBP-201, and calculate the PK characteristics of steady-state trough concentrations of individuals and each group of subjects at each treatment time point.

9.5.4. PD Endpoints

Change in serum IL-4, IL-13, IgE, TARC levels and peripheral blood eosinophil count from baseline.

10. Adverse Events

10.1. Definition of Adverse Events

10.1.1. Adverse Event

Adverse events refer to all adverse medical events that occur after subjects receive the investigational medicinal product, which can be manifested as symptoms, signs, diseases or laboratory test abnormalities, but are not necessarily related to the investigational medicinal product.

10.1.2. Serious Adverse Event

An event will be considered a SAE if the following situations occur:

- Leading to death;
- Life-threatening: The investigator determines that the patient is at immediate risk of death when the event occurs. This definition does not include events that may lead to death if it is assumed to be more serious;
- Requiring hospitalization or prolongation of the original hospital stay;
- Leading to permanent or major disability or incapacitation (ie, significant impairment of the subject's activities of daily living);
- Including congenital abnormalities or birth defects in the offspring of the patient;
- Significant medical events: According to the medical judgment of the investigator, other significant medical events that may endanger the patient and may require medical or surgical intervention to prevent one of the above outcomes.

Hospitalization is defined as any first admission (even less than 24 h) to a hospital or equivalent medical institution. Emergency room visits do not necessarily constitute hospitalization, but the medical importance of the events leading up to emergency room visits should be assessed. In the absence of emergency clinical AEs, hospitalization itself cannot be considered as SAE, including optional admissions for elective surgery, managed admissions for treatment (annual physical examination or routine diagnostic procedures not related to AEs), or admissions to a hospital for pre-existing diseases unrelated to new AEs or the deterioration of pre-existing diseases.

Other significant medical events refer to other situations where medical and scientific judgments must be used to determine whether to expedite the reporting. When a significant medical event may not immediately threaten life or lead to death or hospitalization, but if medical measures are needed to prevent one of the above situations from occurring, it is usually considered serious, such as allergic bronchospasm requiring intensive care, blood cachexia, convulsions without leading to hospitalization, progression to drug dependence or abuse. The above significant medical events should also be regarded as SAEs.

10.1.3. Acquisition of Adverse Event Information

At each study visit, the investigator will ask the patient to obtain any medically relevant changes in their health, and whether they were hospitalized, used any new drugs, or changed the concomitant medication regimens (prescription and over-the-counter drugs).

In addition to patient observations, AEs will be recorded in the eCRF based on any data

collected from the source files and the eCRF (e.g., laboratory tests, physical examination results, medical history, ECG changes) or other documents related to patient safety (e.g., patient diaries). An adverse medical condition that has been assessed to preexist from the screening period to before the administration of the study drug and worsens after the exposure of the study drug should be regarded as an AE. Abnormalities in laboratory tests that have occurred or worsened since the last laboratory assessment and are considered by the investigator to be clinically significant should be regarded as AEs.

10.2. Determination of Severity of AEs

The severity of AEs will be assessed based on the following criteria:

The investigator can use CTCAE V5.0 to assist in determining the severity and clinical significance. Below is the CTCAE classification of AE severity:

- **Grade 1/mild**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2/moderate**: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3/severe or medically significant but not immediately life-threatening:** Hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Grade 4/life-threatening consequences:** Urgent intervention indicated
- **Grade 5/death related to AE.**

Note: CTCAE terms present grades of specific laboratory test abnormalities. Grade 4 laboratory test abnormalities do not automatically indicate life-threatening event. Abnormal laboratory test result should be assessed whether it is regarded as an AE.

AEs not listed in the CTCAE will be graded according to the following methods:

- **Grade 1/mild:** Discomfort is observed but does not interfere with normal daily activities.
- **Grade 2/moderate:** Discomfort sufficient to reduce or affect daily activities.
- **Grade 3/severe:** Inability to work or to perform normal daily activities.
- **Grade 4/life-threatening:** Will be life-threatening immediately.
- **Grade 5/death.**

10.3. Determination of Relationship between AEs and Study Drugs

For all AEs (serious and non-serious), the investigator's causality assessment results must be provided. The investigator must record this causality on the eCRF. The investigator's causality evaluation is to determine whether there is a reasonable possibility that the study drug has caused the AE. In general, facts (evidence) or arguments suggesting the causality should be

provided.

The relationship between AE/SAE and study drug is determined according to the five-category classification, as shown in the table below:

Correlation	Criteria for determination
Related	• There is a reasonable temporal sequence between the occurrence of AE and the medication; • The study drug explains the AE more reasonably than other reasons (e.g., the patient's existing disease, environmental or toxic factors, or other treatments the patient received, etc.); • The AE disappears or lessens after the drug is stopped or the dose is reduced; • The AE meets the known AE types of the suspect drug or its similar drugs; • The AE recurs after re-administration.
Possibly related	• There is a reasonable temporal sequence between the occurrence of AE and the medication; • The study drug explains the AE as reasonably as other reasons (e.g., the patient's existing disease, environmental or toxic factors, or other treatments the patient received, etc.); • The AE disappears or lessens after the drug is stopped or the dose is reduced (if applicable).
Unlikely related	• Other reasons (e.g., the patient's existing disease, environmental or toxic factors, or other treatments the patient received, etc.) explain the AE more reasonably than the study drug; • The AE does not disappear or lessen after the drug is stopped or the dose is reduced (if applicable), or the situation is unclear. • The AE does not recur after re-administration, or the situation is unclear.
Not related	• There is no reasonable temporal sequence between the occurrence of AE and the medication, or; • The AE has other evidence reasons (e.g., the patient's existing disease, environmental or toxic factors, or other treatments the patient received, etc.).
Indeterminable	• The above information is unclear, and the investigator believes that it cannot be judged based on the existing information, and the investigator cannot obtain further follow-up information.

It may happen that although an AE has occurred, very little information is available in theinitial report. However, before transmitting AE data to the sponsor for the first time, it is still very important for the investigator to assess the correlation of the event. The investigator can change his/her view of the correlation based on the follow-up information, and at the same time modify the AE report page and SAE report form (if applicable) in the eCRF accordingly.

The investigator can refer to the Investigator's Brochure for CBP-201 provided by the sponsor, safety findings of similar drugs (e.g., the safety data of dupilumab, a marketed product with the same target), and support correlation judgment based on the study drug’s pharmacological properties and the nature of the disease. For some information, please refer to Section 4 of this protocol.

In this study, AEs whose causality is judged as “related”, “possibly related” and

"indeterminable" will be regarded as adverse drug reactions.

10.4. Investigator's Responsibility for Safety Reports

10.4.1. Principle of AE Reporting

All AEs that occur from the signing of the ICF to the end of the patient's study as specified in the protocol (to the completion of the follow-up visit for early withdrawals). During the entire study period, all AEs must be fully recorded in the source file and transcribed in the eCRF, regardless of whether they are considered drug-related or not.

PTAE is defined as any adverse medical event that occurs after the subject signs the ICF to before receiving the study drug administration, and it is not necessarily causally related to study participation. TEAE is defined as an AE that occurs or worsens during treatment. The treatment period refers to the period from the first study drug administration to the end of the protocol-specified follow-up period.

Laboratory test abnormalities that are not clinically significant will not be recorded as AEs. Abnormal laboratory tests, vital signs, electrocardiogram, and injection site reactions that are clinically significant (ie, "clinically significant abnormalities") should be reported as AEs. If a laboratory test abnormality is part of a syndrome, the AE should be recorded as a syndrome or diagnostic result (e.g., anemia) rather than a laboratory test result (e.g., hemoglobin reduction). Unless related to the study procedure, any medical condition that was present at the time of patient screening but does not deteriorate will not be reported as an AE. However, if it worsens at any time during the study, it should be recorded as an AE.

The investigator should assess and record all AEs, and report diagnostic results or syndromes as much as possible, rather than symptoms. AE-related information should be clearly recorded on the eCRF AE report page, including but not limited to the following:

- AE term
- Start date
- Stop date
- Severity
- Relationship with the study drug
- Action taken with the study drug in response to the AE
- AE outcome

Any adverse event should be followed up until the event resolved/recovered and/or stabilizes, regardless of whether the event is considered to be related to the study drug. If the patient rejects further follow-up, is lost to follow-up, or under other circumstances where the outcome of the event cannot be obtained, relevant information needs to be recorded in the patient's medical record. The MedDRA will be used to code AEs and medical history. In addition, the World Health Organization Drug Dictionary (WHODrug) will be used to code drug usage.

10.4.2. Guidance for the Reporting of Serious Adverse Events

Any SAE that occurs from the signing of the ICF to the end of the patient's study as stipulated in the protocol (to the completion of the follow-up visit for early withdrawals) should be reported, regardless of whether it is related to the study drug.

The SAE must be reported to the sponsor or its designated personnel within 24 hours of receipt. If the SAE is fatal or life-threatening, the sponsor/CRO must be notified immediately, regardless of the extent of information available on the event.

All SAEs must be immediately (within 24 h of being learned) reported to the CRO by email:

Email for SAE reports: PV@tigermedgrp.com

Tigermed's fax for SAE safety reports: 021-33275864

The initial report should include all the information known at the time of the report (additional information can be reported after it is obtained). Do not delay the initial report in order to obtain the outcome or follow-up information.

The investigator reports SAEs by filling in the SAE report form provided by the sponsor/CRO. Usually, it will include a sufficiently detailed description of the AE to allow a complete medical assessment of the case and independent determination of possible causality. Any information related to the event must be provided, such as concomitant drugs and diseases. The SAE report form will include the following information:

- Patient number
- Country where the event occurs
- Event information
- Related test results and laboratory data
- Any other related history
- Action taken with the study drug
- Investigator's assessment of relationship
- Other measures (treatments, etc.)

The medical monitor of the CRO or the designated personnel of the CRO/sponsor can contact the investigator to request additional information of the event or to confirm information. All SAEs will be entered in the AE case report form. The same term should be used in the sponsor's SAE report form and AE case report form. The investigator is responsible for reporting all SAEs to the sponsor (or designated personnel) in a complete and timely manner, reporting follow-up information about SAEs (the SAE follow-up report method is the same as the initial report), and notifying the EC of the occurrence and related details of the event in accordance with local regulations; for reports involving deaths, the investigator should provide the sponsor and the EC with other required information, such as autopsy reports and final medical reports. If there is a problem with whether it is an SAE, the event should be reported.

Any SAE should be followed up until the event has resolved/recovered or stabilized, so follow-

up may continue beyond the last visit planned by the protocol, and the sponsor's monitoring team may require additional inspections. At any time after the end of the study, any serious adverse event noticed by the investigator should be reported to the monitoring team or the sponsor/designated personnel within 24 h if he/she believes that there is a reasonable possibility that it has been caused by the study drug.

10.4.3. AE of Special Interest

AESIs refer to the sponsor's product or project-specific AEs (serious or non-serious) that require scientific and medical attention and require continuous monitoring, which should be notified by the investigator to the sponsor by email. Further research may be required to characterize and understand these events, and these events should be marked as “AESI” in the eCRF. During the study period, AESI can be added or removed through protocol clarification or revision.

Conjunctivitis and keratitis were events of interest in the research experience of dupilumab. Akinlade 2019 [33] reported that in the combined experience of dupilumab in the treatment of patients with AD (n=1047), a total of 90 patients (8.6%) reported at least one “conjunctivitis” AE, while among patients in the placebo group (n=517), 11 cases (2.1%) of such events were reported. The severity of conjunctivitis AEs was mostly mild to moderate, and severe events were reported by ≤0.5% of patients in the dupilumab combined group and ≤0.3% of patients in the placebo group. In the dupilumab group, 2 patients permanently discontinued study drug due to conjunctivitis. Conjunctivitis usually occurred between Week 4 and Week 8, and events became less common after long-term treatment. Conjunctivitis was more common in patients with severe AD at baseline, patients with a previous history of conjunctivitis, and patients with high baseline TARC and IgE levels. The combined dupilumab data indicate that the incidence of conjunctivitis may decrease as the trough concentration of dupilumab increases.

This pattern has not been observed in studies of other indications for dupilumab, including asthma and chronic sinusitis with nasal polyps.

Based on lessons from the experience of dupilumab in the treatment of AD, the ophthalmology adverse events “conjunctivitis” and “keratitis” will be regarded as AESIs, which should be evaluated by an ophthalmologist if the investigators or sponsor consider necessary and appropriate treatment should be given until it is resolved.

In addition to conjunctivitis and keratitis, the following AEs are also classified as AESIs, including serious immediate hypersensitivity, all reactions at injection site which persist over 24 h, AST/ALT increased>5× ULN, parasitic and opportunistic infection, pregnancy and symptomatic overdoses.

The immediate hypersensitivity will be defined according to the symptoms described in Sampson et al. 2006 [34], as follows:

Should any one of the following 3 criteria be met, the immediate hypersensitivity is likely to

occur:

1. Acute onset (minutes to several hours) of certain illness with involvement of the skin or mucosal tissue, or both (eg, generalized hives, pruritus or Hushing, swollen lips-tongue-uvula) and associated with at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, PEF decreased, hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., , hypotonia (collapse), syncope, incontinence)
2. Two or more of the following that occur after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., , generalized hives, itching-flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, PEF decreased, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., cramping abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours); systolic blood pressure (SBP) lower than 90 mmHg or reduction from baseline greater than 30%;

Whether the infection is classified as opportunistic infection will be determined after discussion with medical monitors. When reporting opportunistic infection, the investigators will take Winthrop et al. 2015 [35] as reference.

10.4.4. Pregnancy Report

For all pregnancies of the female subjects participating in the study and the female partners of the male subjects determined from the subject's first drug administration to 8 weeks after the last dose of study drug, the investigator must report to the medical monitor and the sponsor within 24h by using the **pregnancy report form** provided by the sponsor/CRO. The patient will be asked to provide information about the outcome of the pregnancy, including early termination (selective abortion). Abnormal pregnancy outcomes such as spontaneous abortion and congenital abnormalities will be reported as SAEs, and an SAE form should be submitted. Pregnancy itself is not an SAE. Female patients who become pregnant during the study period and after randomization must immediately withdraw from the study drug treatment and be followed up to the pregnancy outcome, including delivery or termination of pregnancy. Every effort should be made to follow up the pregnancy until the end of the pregnancy. If possible, the investigator will follow the delivery for 4 weeks to observe possible congenital

abnormalities. The pregnancy of a male patient's partner is not considered an AE, and the male patient should not withdraw from the study. If the partner of a male patient becomes pregnant during this period (from the first dose to 8 weeks after the last dose), the investigator will notify the sponsor and the EC, and provide appropriate medical follow-up with the consent of the partner.

10.5. Sponsor's Responsibility for Safety Reports

The sponsor will monitor and assess the safety of the study drug during the study period, manage and report all AE in accordance with all applicable regulations, and include them in the final clinical study report. All suspected unexpected SAEs (SUSAR) that are reasonably related to the study drug should be reported to the investigator, clinical trial institution/EC, drug regulatory authority, and competent health authority.

10.5.1. Suspected Unexpected Serious Adverse Reactions

Before an SAE is determined as a suspected unexpected serious adverse reaction (SUSAR), the SAEs and SUSAR should be handled in the same way. The investigator should report all SAEs within the agreed time limit to the sponsor.

If the nature and severity of the AE is inconsistent with the existing information provided by the sponsor, such as the Investigator's Brochure for the study drug, the package insert of the marketed drug, or the summary of product characteristics, it is an "unexpected" AE. Since CBP-201 has not yet been approved for marketing, information related to the study drug can be found in the Investigator's Brochure. For unexpected events where the investigator or sponsor judges that there is a reasonable possibility that the SAEs have been caused by the study drug, the sponsor will expedite the report in accordance with the relevant requirements of the *Good Clinical Practice for Pharmaceuticals* (2020 Edition):

- After receiving the safety-related information from any source, the sponsor shall immediately analyse and assess it, including the severity, correlation with the study drug, and whether it is an expected event. The sponsor shall promptly report SUSAR to all investigators and clinical trial institutions participating in the clinical trial and the Ethics Committee; the sponsor shall report SUSAR to the drug regulatory authority and the competent health authority.
- After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigator should sign and read it in time, and consider the treatment of the subject and whether to make corresponding adjustments, communicate with the subject as soon as possible if necessary, and report the SUSAR provided by the sponsor to the EC.
- According to the *Standards and Procedures for Rapid Reporting of Safety Data during Drug Clinical Trials*, for fatal or life-threatening SUSARs, the sponsor should report as soon as possible after being first notified, but no more than 7 days, and report and improve follow-up information within the following 8 days. For non-fatal

or life-threatening SUSAR, the sponsor should report it as soon as possible after first being notified, but no more than 15 days.

The sponsor will conduct regular and annual reports in accordance with the requirements of laws and regulations.

11. Data Management

11.1. Data Management Process

The data management of this study is in the charge of the CRO's Data Department to ensure the authenticity, completeness, privacy and traceability of clinical research data. The detailed data management procedures will be described in a separate data management plan.

11.2. Data Collection

Data will be collected through an electronic data collection system (EDC). The investigator or the site staff authorized by the investigator will enter the subject data into the eCRF. The investigator or the staff authorized by the investigator will receive appropriate training and take appropriate information security measures before the initiation of the study site or data entry. The investigator should supervise the data collection at the study site. The investigator should ensure that all clinical trial data are obtained from clinical trial source files and trial records, and are accurate, complete, readable and timely. The source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, and enduring. The modification of the source data should leave trails, the original data should not be concealed, and the reason for the modification should be recorded.

Unless otherwise specified, eCRF will only be used as a form for collecting data and cannot be used as original materials. Source documents refer to the original records, documents and data generated in this study, such as hospital medical records, medical images, laboratory records, memos, subject diaries or assessment forms, drug distribution records, data automatically recorded by instruments, X-rays, subject files, clinical trial-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies. The source file includes the source data, which can exist in paper or electronic forms. In order to avoid differences in assessments between different assessors, it is necessary to ensure that the baseline and all subsequent efficacy and safety evaluations of the same subject are completed by the same assessor.

The investigator is responsible for maintaining all original documents and ensuring that they are monitored by the CRA at each visit. In addition, the investigator is required to submit a complete eCRF for each subject participating in the study, regardless of the length of time the subject has participated in the study, carefully verify the study number and subject number of all supporting documents (such as laboratory records or study site records) submitted with the eCRF, and delete all personal private information (including the subject's name) or make it illegible to protect the privacy of subjects.

11.3. Database Design

The eCRF is constructed in the EDC system by the CRO's Data Department, and the process should meet the requirements of the FDA 21 CFR Part 11. The database should manage the system login, data entry, modification, deletion and other data traces, and the establishment of

the database should adopt the standards of the Clinical Data Interchange Standards Consortium (CDISC).

The sponsor should have written procedures to ensure that their changes to eCRF are necessary, recorded, and approved by the investigator. The investigator should keep records of revisions and corrections.

11.4. Data Entry and Modification

The investigator or the site staff authorized by the investigator should fill in and modify the eCRF in accordance with the instructions provided by the CRO's Data Department. The CRA does not have this authority. The investigator should ensure that the data in various eCRF and other reports is accurate, complete, clear and timely. All data should be entered into the EDC during the visit or as soon as possible after the visit, and data entry should be carried out in strict accordance with the principle of "what you see is what you record". The EDC must be kept up-to-date to ensure that it reflects the latest dynamics of the subjects. If certain assessments are not carried out during the study, or certain information is unavailable, inapplicable or unknown, the investigator or the authorized site staff should record it in the eCRF.

The data in eCRF will be delivered to the data server. The investigator must review the data to ensure the accuracy and correctness of all entered data, and electronically sign the verified data. The signed information (including the date of signing) will be stored in the audit trail and shall not be changed.

The data in the eCRF should be consistent with the source file. If there is any inconsistency, a reasonable explanation should be made. Any correction or modification of eCRF made by the investigator or the authorized site staff should make the initial record clear and identifiable, keep the modification trails, explain the reason if necessary, and sign and date the modification. Change to the data that have been approved require the investigator to electronically sign again.

11.5. Data Verification

According to the finalized data verification plan, data manager will set up a data logic check program in the EDC system.

After the data is entered into the EDC system, the data will be verified through computer logic check and manual verification to ensure the logic, consistency and accuracy of the data.

After the data is entered into the EDC system, if there is any data that does not conform to logic, the system logic check will start operation and trigger a query. These queries need to be reviewed and answered by the investigator or personnel authorized by the investigator. When the updated data makes the logic check no longer valid, the data query will be immediately closed; when the study site confirms the data and provides a response, data manager needs to review and respond to the information. If the reason provided by the study site is reasonable, the data query will be closed; if the data problem is not resolved, data manager can continue to

communicate with the study site by continuing to add data queries until the data problem is finally resolved.

The subject data list/report is generated by programming to support manual data verification throughout the research process. When any data needs to be clarified/verified/confirmed by the investigator, manual queries can be added to the EDC system. These queries will be manually closed after the data is corrected or confirmed. The query will be recorded in the audit trail of the EDC system, including the operator's name, time and date.

The data manager should ensure that all queries are resolved before the database is locked, and the investigator should complete all electronic signatures in the EDC system to ensure the completeness and accuracy of the subject data in the EDC system.

11.6. Medical Coding

The data manager of the CRO's Data Department is responsible for the medical coding work of this study. The coding content includes medical history, AE, prior/concomitant medication, and prior/concomitant non-drug treatment.

Medical history and AEs will be coded according to the MedDRA (Version 22.1 or above) and submitted in the form of System Organ Class (SOC) and preferred terms. Prior medications and concomitant/concurrent medications will be coded using the World Health Organization Drug Dictionary (WHODD) (September 2018 version or above), and only the versions confirmed by the sponsor will be used for all dictionaries.

During the coding process, if there is a problem that any data cannot be coded due to improper, inaccurate, or vague medical terms, data manager will ask the investigator to verify and confirm by way of data queries.

Before the database is locked, data manager should send a medical coding report to the sponsor, which must be reviewed by the sponsor.

11.7. Data Locking

After reviewing and confirming that the established database is correct, the principal investigator, the sponsor, and the statistician will jointly decide to lock the database, and data manager will lock the database in the EDC system. In principle, the locked database is not allowed to be changed. If any data that needs to be modified is discovered after the data is locked, the main principal investigator, the sponsor, the statistician and data manager must agree to unlock the database before modifying it, and save written records and signatures of all parties.

12. Statistical Analysis

12.1. Statistical Analysis Plan

This section explains the statistical methods used for safety and efficacy analysis. The final analysis methods and specific details will be recorded in the official Statistical Analysis Plan

(SAP), where PK and PD analyses will be described separately in a PK/PD SAP. The SAP will be completed before the database is locked, and include detailed information on how to generate variables, how to handle missing data, and how to present the data, as well as detailed information on statistical methods used for safety and efficacy analysis. The final clinical study report will discuss deviations from the SAP (if any).

12.2. Statistical Hypothesis

Primary hypothesis:

H0: There is no efficacy difference between the CBP-201 300 mg Q2W group and the placebo group at W16 of treatment;

H1: There is an efficacy difference between the CBP-201 300 mg Q2W group and the placebo group at W16 of treatment.

12.3. Basis of Sample Size

The sample size of 255 cases (in a 2:1 ratio, 170 cases in the CBP-201 300 mg Q2W group, and 85 cases in the placebo group. Assuming that the dropout rate in the treatment group is 15%, then about 144 cases in the CBP-201 300 mg Q2W group and 72 cases in the placebo group will be able to complete the study) can provide a power of 90% to detect the therapeutic effect on the primary endpoint in the CBP-201 300 mg Q2W group and the placebo group. This power is calculated based on the following assumption: the proportion of subjects reaching the primary efficacy endpoint is 27% in the CBP-201 300 mg Q2W group and 9% in the placebo group, and the significance level for two-sided tests is 0.05.

Based on the results of another conducted phase II international multicenter clinical study of CBP-201 in patients with moderate-to-severe atopic dermatitis, the proportion of subjects reaching the primary efficacy endpoint was 28.1% in the CBP-201 300mg Q2W group and 10.7% in the placebo group, at a two-sided test significance level of 0.05, and if the results of this trial are similar to that of the WW001 trial, the above sample size would provide a power of more than 85% to detect the therapeutic effect on the primary endpoint between the CBP-201 300 mg Q2W group and the placebo group. Therefore, no adjustment is made to the sample size.

The primary analysis of this study will still be based on the 255 subjects enrolled in accordance with V2.1 and its earlier versions of the protocol. Subjects newly enrolled (approximately 81 cases) based on the protocol after V2.1 will not be included in the primary analysis, and only supplementary analysis will be performed.

12.4. Analysis Populations

In this study, it is planned to perform statistical analyses in two stages:

First of all, after the 255 subjects enrolled based on the V2.1 and prior versions of the protocol complete the administration and treatment, related evaluations and follow-up of Stage 1 (W16

pre-dose visit), the primary analysis will be performed based on the data of the 255 subjects, and the following 6 analysis populations are defined as:

- Screening set 1 will include all subjects who have signed the ICF.
- Randomization set 1 will include all subjects randomized at baseline (D1), regardless of whether they have received the treatment of study drug.
- Full analysis set 1 (FAS1) will include all subjects in randomization set 1 who have received at least one dose of the study drug. FAS1 will determine the treatment groups based on the planned treatment.
- Per protocol set 1 (PPS1) will include all subjects in FAS1 without any major protocol deviation.
- Safety set 1 (SS1) will include all subjects who have received at least one dose of the study drug. SS1 will determine the treatment groups based on the actually received treatment.
- PK set 1 (PKS1) will include subjects in randomization set 1 who have received at least one dose of CBP-201 active drug and had at least 1 collected and analyzable PK sample.

After all subjects (including approximately 81 additional subjects enrolled) entering Stage 2 have completed the treatment, evaluations and follow-up of Stage 2, a Stage 2 analysis will be performed. The Stage 2 analysis will be defined as the following 6 analysis populations:

- Randomization set 2 will include all subjects entering Stage 2, including all subjects who are randomized into Group C or Group D, and subjects entering Group E.
- Full analysis set 2 (FAS2) will include all subjects in randomization set 2 who have received at least one dose of study drug in Stage 2. FAS2 will determine the treatment groups based on the planned treatment.
- Per protocol set 2 (PPS2) will include all subjects in FAS2 without any major protocol deviation.
- Safety set 2 (SS2) will include all subjects in randomization set 2 who have received at least one dose of study drug in Stage 2. SS2 will determine the treatment groups based on the actually received treatment.
- Safety set 3 (SS3) will include all subjects in SS1 and SS2 who have received at least one dose of the study drug.
- PK set 2 (PKS2) will include subjects who have received at least one dose of CBP-201 active drug in Stage 2 and had at least 1 collected and analyzable PK sample.

At stage 2, for subjects in group C or group D who have not achieved EASI-50 and are therefore assigned to group E to receive subcutaneous injection of CBP-201 300 mg every 2 weeks, their

efficacy variables and safety variables will be analyzed by assigned treatment groups or actual treatment groups and by stages.

The detailed definition of the statistical analysis data sets will be supplemented or adjusted in the SAP.

12.5. Analysis Plan

Statistical analyses will be performed using SAS 9.4 or higher version.

Descriptive statistics will be used to summarize demographics, baseline characteristics, exposure, safety data, PK and PD data. For continuous variables, descriptive statistics will include the number of observed subjects, the number of subjects with missing observations, mean, SD, standard error, minimum, median, maximum, frequency, and percentage. For lognormally distributed data, the geometric mean, geometric standard deviation and geometric coefficient of variation will be calculated. For categorical variables or ordinal data, the frequency and percentage of each category will be listed.

For changes in continuous variables from baseline, the results will be presented according to their corresponding post-baseline visits. All research data and other clinically significant data used to generate tables and figures will be listed by treatment group, subject, and time point.

Definition of baseline:

Primary analysis: The baseline of efficacy analysis is defined as the last available value before randomization in Stage 1, and the baseline of safety analysis is defined as the last available value before the first dose in Stage 1.

Stage 2 analysis: Two sets of baselines are defined.

- The first set of baselines: the baseline of efficacy analysis is defined as the last available value before randomization in Stage 1, and the baseline of safety analysis is defined as the last available value before the first dose.
- The second set of baselines: The baseline of efficacy analysis is defined as the last available value before randomization in Stage 2 or before entering Group E, and the baseline for safety analysis is defined as the last available value before the first dose in Stage 2.

After the 255 subjects enrolled based on the V2.1 and prior versions of the protocol complete the administration and treatment, related evaluations and follow-up of Stage 1 (W16 pre-dose visit), the primary analysis will be performed.

For subjects entering stage 2 study, analyses will be performed based on the baseline of the two groups.

During the primary analysis, the W16 data will be unblinded and statistically analyzed. The statistically significant type I error level of the primary efficacy endpoint analysis is set at 0.05 (two-sided test).

After all subjects (including approximately 81 additional subjects enrolled) entering Stage 2 have completed the treatment, evaluations and follow-up of Stage 2, a Stage 2 analysis will be performed. Statistical inference will not be performed during the Stage 2 analysis.

12.6. Study Subjects and Demographics

12.6.1. Disposition and Withdrawal

The number of subjects who have failed screening (along with the reason), been randomized, completed the study, and early terminated the study (along with the reason for ET) will be summarized in the table and classified by treatment group. The number of subjects in each analysis population will be reported.

12.6.2. Protocol Deviations

Before the database is locked, all protocol deviations will be classified and recorded, and discussed in the CSR. All protocol deviations (including minor deviations and major deviations) will be listed in the data listings.

12.6.3. Demographics and Other Baseline Characteristics

Demographic data and baseline characteristics (including age, gender, weight, and height) will be summarized for each treatment group and the overall population using descriptive statistics. Demographic characteristics and baseline characteristics will be listed and summarized. The medical history and clinical laboratory test results at the time of screening will be listed.

Prior medications and concomitant medications will be summarized by treatment group and the number and percentage of subjects who have used each drug, and classified by using the World Health Organization Drug Dictionary's Anatomical, Therapeutic, and Chemical Classification (WHO ATC) and preferred terms.

12.6.4. Exposure

This study is a 2-stage repeated dosing study, and the study treatment dosing will be summarized according to the study stage and treatment regimen group.

12.7. Efficacy Endpoint Analysis

12.7.1. Test Strategies

In order to control the probability of type I error in multiple comparison, a fixed-sequence method (based on the sequence for key secondary endpoints listed in this protocol) will be used. First of all, comparison of primary efficacy endpoint will be made between the treatment group and the placebo group. If the efficacy of primary efficacy endpoint is statistically significant, the comparison of key secondary efficacy endpoints between treatment group and the placebo group will be made based on the sequence specified in the protocol.

12.7.2. Estimand and Intercurrent Events

Table 12.1 Intercurrent Events

Label	Intercurrent event	Strategy	Remarks
Intercurrent event 1 (use of prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated due to poor treatment effect)	· Dupilumab or any anti-IL-4Rα or IL-13 antibodies; · Topical PDE-4 inhibitors or JAK inhibitors; · Systemic treatment with corticosteroids or other immunosuppressive and/or immunomodulatory agents, such as cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, or oral JAK inhibitors; · Cell depletion agents (e.g., Rituximab) or other biological agents; · Other investigational drugs (non CBP-201) or treatments. Due to the poor treatment effect, the above prohibited drugs/treatments have been used before the W16 visit.	Composite strategy	This type of intercurrent event occurs because of poor treatment effect, and should be treated as non-response. If it is a continuous variable, the data after the occurrence of the intercurrent event should be imputed with WOCF.
Intercurrent event 2 (use of other prohibited drugs/treatments specified in the protocol other than those in Intercurrent Event 1, with a negligible impact on the assessment of the primary endpoint)	· Initiation of SIT or dose up-regulation; · TCS or TCI; · Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies; · Bleaching baths more than 2 times a week; · Any drug (except mild emollients) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity. The cumulative duration of use of the above prohibited drugs/treatments before the W16 visit is no more than 7 days, and the end date is at least 4 weeks away from the W16 visit.	Treatment policy strategy	The impact on the assessment of efficacy endpoints can be ignored, and the actual observed value is used. If the actual observed value is missing, it will be processed according to the principle for processing missing values.
Intercurrent event 3 (use of other prohibited drugs/treatments specified in the protocol other than those in Intercurrent	· Initiation of SIT, or dose up-regulation; · TCS or TCI; · Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies; · Bleaching baths more than 2 times a week; · Any drug (except mild emollients) that may interfere with the evaluation of efficacy results or affect the evaluation of AD	Composite strategy	This type of intercurrent event occurs because of poor treatment effect, and should be treated as non-

Label	Intercurrent event	Strategy	Remarks
Event 1 due to poor treatment effect, with a major impact on the assessment of the primary endpoint)	severity. The cumulative duration of use of the above prohibited drugs/treatments before the W16 visit is more than 7 days, or the end date is less than 4 weeks away from the W16 visit.		response. If it is a continuous variable, the data after the occurrence of the intercurrent event should be imputed with WOCF.
Intercurrent event 4 (early termination of treatment/EOT due to adverse events)	The subject experiences an AE or SAE that is considered by the investigator to be intolerable before the W16 visit, and is unsuitable for continuing the study treatment, resulting in early termination of treatment/EOT.	Composite strategy	This type of intercurrent event occurs because of poor safety of treatment, and should be treated as non-response. If it is a continuous variable, the data after the occurrence of the intercurrent event should be imputed with WOCF.
Intercurrent event 5 (the subject's administration is missing due to the COVID-19 epidemic)	The administration at two consecutive visits immediately before the W16 visit is missing or the administration in the Stage 1 treatment period is missing for ≥3 times.	Hypothetical strategy	The actual observed values are not used, and the J2R (jump to reference) method is used for imputation.

Table 12.2 Definition of Estimand for the Primary Endpoint and Strategies for Managing Intercurrent Events

Primary objective	To assess the efficacy of CBP-201 in subjects with moderate to severe AD
Label of estimand	Estimand of primary endpoint

Description of Estimand	A patient is considered as treatment success if: The patient has an IGA score of 0-1 which is decreased by ≥ 2 points from baseline at W16. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the primary endpoint due to poor treatment effect, or has early termination of treatment/EOT due to adverse events.
Target population	Patients aged 12 years and older with moderate to severe AD and weighing ≥40 kg
Primary endpoint	1) IGA score is 0 or 1 at W16, and improved by at least 2 grades from baseline at W16; 2) A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the primary endpoint due to poor treatment effect, or has early termination of treatment/EOT due to adverse events.
Study treatment	・ The subjects will receive a subcutaneous injection of CBP-201 600 mg (4 ml) on Day 1, begin to receive a subcutaneous injection of CBP-201 300 mg (2 ml) from Week 2 (W2), and receive treatment at the same dose every 2 weeks thereafter until W14; ・ The subjects will receive a subcutaneous injection of placebo 4 ml on Day 1, begin to receive a subcutaneous injection of placebo 2 ml from W2, and receive placebo 2 ml every 2 weeks thereafter until W14.
Population-level summary	The difference in the proportion of subjects whose IGA score is 0-1 and decreased by ≥2 points from baseline at W16 between the CBP-201 group and the placebo group.
Strategies for Managing Intercurrent Events	
Intercurrent event 1 (use of prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated due to poor treatment effect)	Composite strategy
Intercurrent event 2 (use of other prohibited drugs/treatments specified in the protocol other than those in Intercurrent Event 1, with a negligible impact on the assessment of the primary endpoint)	Treatment policy strategy
Intercurrent event 3 (use of other prohibited drugs/treatments	Composite strategy

specified in the protocol other than those in Intercurrent Event 1 due to poor treatment effect, with a major impact on the assessment of the primary endpoint)	
Intercurrent event 4 (early termination of treatment/EOT due to adverse events)	Composite strategy
Intercurrent event 5 (the subject's administration is missing due to the COVID-19 epidemic)	Hypothetical strategy
Rationale for the strategies	The primary objective of the trial is to prove the clinical efficacy of CBP-201 compared with placebo in patients aged 12 years and older with moderate to severe AD and weighing ≥40 kg. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the primary endpoint due to poor treatment effect, or has early termination of treatment/EOT due to adverse events. For cases in which subjects are affected by the COVID-19 epidemic to result in missing administrations that will affect the assessment of efficacy (ie, intercurrent event 5), subsequent data will no longer be used.

Table 12.3 Definition of Estimand for Key Secondary Endpoints and Strategies for Managing Intercurrent Events

Label of estimand	Estimand of key secondary endpoints
Description of estimand	• Achieving EASI-75 at W16; • Weekly average PP-NRS decreased by ≥ 4 points from baseline at W16; • Weekly average PP-NRS decreased by ≥ 3 points from baseline at W16; • Change and percentage change in the weekly average PP-NRS from baseline at W16; • Achieving EASI-90 at W16. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the key secondary endpoints due to poor treatment effect, or has early termination of treatment/EOT due to adverse events. In this case, continuous variables should be imputed with WOCF.
Target population	Patients aged 12 years and older with moderate to severe AD and weighing ≥40 kg
Key secondary endpoints	• The proportion of subjects achieving EASI-75 at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 4 points from baseline at W16;

	• The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 3 points from baseline at W16; • Change and percentage change in the weekly average PP-NRS from baseline at W16; • The proportion of subjects achieving EASI-90 at W16.
Study treatment	The subjects will receive a subcutaneous injection of CBP-201 600 mg (4 ml) on Day 1, begin to receive a subcutaneous injection of CBP-201 300 mg (2 ml) from Week 2 (W2), and receive treatment at the same dose every 2 weeks thereafter until W14; The subjects will receive a subcutaneous injection of placebo 4 ml on Day 1, begin to receive a subcutaneous injection of placebo 2 ml from W2, and receive placebo 2 ml every 2 weeks thereafter until W14.
Population-level summary	The differences in the following endpoint measures between the CBP-201 group and the placebo group: • The proportion of subjects achieving EASI-75 at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 4 points from baseline at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 3 points from baseline at W16; • Change and percentage change in the weekly average PP-NRS from baseline at W16; • The proportion of subjects achieving EASI-90 at W16.
Strategies for Managing Intercurrent Events	
Intercurrent event 1 (use of prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated due to poor treatment effect)	Composite strategy
Intercurrent event 2 (use of other prohibited drugs/treatments specified in the protocol other than those in Intercurrent Event 1, with a negligible impact on the assessment of the primary endpoint)	Treatment policy strategy
Intercurrent event 3 (use of other prohibited drugs/treatments specified in the protocol other than those in Intercurrent Event 1 due to poor treatment effect, with a major impact on the assessment of the primary endpoint)	Composite strategy
Intercurrent event 4 (early termination of treatment/EOT due to adverse events)	Composite strategy
Intercurrent event 5 (the subject's	Hypothetical strategy

administration is missing due to the COVID-19 epidemic)	
Rationale for the strategies	The primary objective of the trial is to prove the clinical efficacy of CBP-201 compared with placebo in patients aged 12 years and older with moderate to severe AD and weighing ≥40 kg. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the key secondary endpoints due to poor treatment effect, or has early termination of treatment/EOT due to adverse events. Continuous variables should be imputed with WOCF. For cases in which subjects are affected by the COVID-19 epidemic to result in missing administrations that will affect the assessment of efficacy (ie, intercurrent event 5), subsequent data will no longer be used.

12.7.3. Overview of Statistical Methods: Estimation of Estimand and Sensitivity Analysis

Table 12.4 Summary of Statistical Methods and Sensitivity Analysis for the Primary Endpoint and Key Secondary Endpoints

Label of estimand	Description of estimand	Main estimator			Sensitivity/ Supplementary analysis
		Analysis sets	Rules for imputation	Model/method for the main analytical methods	
Estimand of the primary endpoint	The difference in efficacy in patients aged 12 years and older with moderate to severe atopic dermatitis and weighing > 40 kg between the CBP-201 300 mg Q2W group and placebo group. A patient is considered as treatment success if the patient has an IGA score of 0-1 which is decreased by ≥ 2 points from baseline at W16. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the primary endpoint due to poor treatment effect, or has early termination of treatment/EOT due to adverse events.	FAS (will include all subjects in Randomization Set 1 who have received the study drug at least once.)	For subjects who experience intercurrent events, their visits after the intercurrent events will be handled in accordance with the strategies for managing intercurrent events listed in Table 12.1 and Table 12.2. If the target variable is still missing after application of the strategies for managing intercurrent events, the multiple imputation (MI) method will be used to impute the missing data in the placebo group, and the J2R (jump to reference) method will be used to impute the missing data in the CBP-201 group. The detailed methods will be specified in the SAP.	Differences in response rates between the treatment group and placebo group and their 95% confidence intervals will be analyzed using the Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA 3 or 4). The Type I error level for statistical significance of the difference in response rates between CBP-201 and placebo is set at 0.05 (two-sided test).	**Sensitivity analysis 1:** When the target variable is still missing after application of the strategy for managing intercurrent events, it will be classified as treatment failure. **Sensitivity analysis 2:** When the target variable is still missing after application of the strategy for managing intercurrent events, tipping point analysis will be used for analysis. **Supplementary Analysis 1:** Primary analysis will be performed using the PPS. **Supplementary analysis 2:** The treatment policy strategy will be used for all intercurrent events; the FAS will be used, and the missing data will be subject to the

					imputation rules of the main estimator, that is, the multiple imputation method (MI) will be used to impute the missing data in the placebo group, and the J2R (jump to reference) method will be used to impute the missing data in the CBP-201 group.
Estimand of key secondary endpoints	The differences in the following measures in patients aged 12 years and older with moderate to severe AD and weighing ≥40 kg between the CBP-201 300mg Q2W group and the placebo group: • The proportion of subjects achieving EASI-75 at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 4 points from baseline at W16; • The proportion of subjects whose weekly average PP-NRS is decreased by ≥ 3 points from baseline at W16; • Change and percentage change in the weekly	FAS (will include all subjects in Randomization Set 1 who have received the study drug at least once.)	For subjects who experience intercurrent events, their visits after the intercurrent events will be handled in accordance with the strategies for managing intercurrent events listed in Table 12.1 and Table 12.3. If the target variable is still missing after application of the strategies for managing intercurrent events, the multiple imputation (MI) method will be used to impute the missing data in the placebo group, and the J2R (jump to reference) method will be used to impute the	For categorical variables, differences in response rates between the treatment group and placebo group and their 95% confidence intervals will be analyzed using the Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA 3 or 4). For continuous variables, analysis will be performed using an MMRM model that will include treatment group, baseline disease severity (IGA 3 or 4), baseline value of the corresponding endpoint, visit, interaction of visit and treatment group, and the LSMEAN estimate values and their 95% confidence	**Sensitivity analysis 1:** When the target variable is still missing after application of the strategy for managing intercurrent events, categorical variables will be classified as treatment failure. Continuous variables should be imputed with WOCF. **Supplementary Analysis 1:** Primary analysis will be performed using the PPS. **Supplementary analysis 2:** The treatment policy strategy will be used for all intercurrent events; the FAS will be used, and the missing data will be subject to the imputation rules of the main

	average PP-NRS from baseline at W16; • The proportion of subjects achieving EASI-90 at W16. A patient should be regarded as treatment failure if he/she uses prohibited drugs/treatments specified in the protocol for which the study treatment must be early terminated or other rescue therapy that has a major impact on the assessment of the key secondary endpoints due to poor treatment effect, or has early termination of treatment/EOT due to adverse events. Continuous variables should be imputed with WOCF.		missing data in the CBP-201 group. The detailed methods will be specified in the SAP.	intervals will be summarized.	estimator, that is, the multiple imputation method (MI) will be used to impute the missing data in the placebo group, and the J2R (jump to reference) method will be used to impute the missing data in the test group.

12.7.4. Subgroup Analysis

For the primary endpoints and key secondary endpoints, subgroup analysis will be performed by baseline characteristics of subjects (e.g., age, severity of disease at baseline, etc.) using the same methodology as the main estimator.

12.8. Safety Analysis

Safety results will be summarized by treatment group. All safety analyses will be performed on SS1 or SS2. AEs will also be analyzed in all subjects who have received at least one dose of study drug in SS3. Safety analyses include TEAEs, AESIs, SAEs, TEAEs at the injection site, eye examination results, laboratory tests, VS, PE, 12-lead ECG results, and ADA test results. Safety data will be summarized by Frequency Tables (counts and percentages) and, where applicable, presented by treatment and scheduled time. The data will be compared with the reference range provided to check for abnormalities and/or clinically relevant changes from baseline (where applicable). In addition, subgroup analysis of part of safety endpoints will be analyzed by age groups(≥18 years and <18 years).

Treatment-emergent adverse event (TEAE)

AEs will be classified in accordance with the terms of Medical Dictionary for Regulatory Activities (MedDRA). The incidence table and the number (n) and the percentage (%) of patients with TEAEs in each treatment group will be provided according to the system organ class (SOC) (sorted according to the internationally agreed order) and preferred term (PT) (in alphabetical order). Multiple occurrences of the same event in the same patient are counted only once in the table during the treatment period. The denominator of the percentage calculation is the safety population in each treatment group.

According to SOC and PT, the severity of TEAE in each treatment group and the correlation with study drug will be summarized.

TEAEs at the injection site will be summarized in the same way.

The number (%) of patients with at least one treatment-emergent SAE will be summarized by treatment group, and displayed by major SOC and PT (in alphabetical order). SAEs will be listed by treatment group and patient.

The number (%) of patients with at least one TEAE that leads to permanent discontinuation of treatment will be summarized by treatment group (%), and displayed by major SOC and PT (in alphabetical order). The TEAEs that lead to permanent discontinuation of treatment will be listed by treatment group and patient.

According to AESI category and PT, the total number of patients (%) who have experienced AESI during treatment will be displayed in a descending order of the incidence of PT in each AESI category.

Safety laboratory tests

Descriptive statistics will be used to summarize the baseline value of laboratory test results and the changes from baseline to each visit.

- According to laboratory-wide specifications, clinical laboratory parameters will be classified into low, normal, or high, and the number and percentage of subjects in each category will be summarized.
- Shift tables based on normal/abnormal baseline values and other tabular and graphical methods may be used to display the results of laboratory tests of interest.
- Lists with flags that indicate values outside the laboratory's range will be provided.

Vital signs

Descriptive statistics will be used to summarize the baseline values of vital signs (body temperature, pulse, blood pressure, and respiratory rate) and the changes from baseline to each visit.

Other safety data, including eye examination results, PE, 12-lead ECG results, and ADA test results will be classified and summarized, and the frequency and percentage of each category will be listed.

12.9. PK Analysis

If applicable, descriptive statistics will be used to summarize individual blood drug concentrations by treatment and scheduled time, or plot a curve of means over time.

12.10. PD Analysis

Descriptive statistics will be used to summarize changes in serum IL-4, IL-13, IgE, TARC levels and peripheral blood eosinophil counts by treatment and scheduled time, and where applicable, plot the mean and SD change curves in each treatment group.

12.11. Data Convention

If the start date of an AE or concomitant medication is incomplete or missing, it is assumed that the AE has occurred during or after the use of the study drug, unless the incomplete date (e.g., month and year) clearly shows that the event began before treatment. If part of the date indicates the same month or year as the study drug use date, the start date of the AE is imputed according to the study drug use date. Otherwise, the missing day or month is imputed according to the first day or month.

Missing laboratory data, ECG data, vital signs data, physical examination and other safety data will not be imputed.

12.12. Interim Analysis

No interim analysis is planned for this study.

13. Clinical Trial Management

13.1. Statement

This clinical trial will be conducted in accordance with the standard operating procedures of the sponsor and the CRO. These SOPs are designed to ensure that the trial complies with the *Declaration of Helsinki* (2017 Edition), the *Guidelines for Good Clinical Practice* promulgated by ICH, the *Good Clinical Practice for Pharmaceuticals* promulgated by the NMPA, and the requirements of drug clinical trial regulations.

When signing the protocol, the investigator will agree to conduct the study in strict accordance with the protocol, clinical trial specifications, and relevant laws and regulations, and keep all the information provided by the sponsor in accordance with confidentiality requirements.

13.2. Ethics

13.2.1. Ethical Implementation/Approval of the Study

The clinical study protocol must be reviewed and approved by the EC of each study site before implementation. The sponsor and the investigator should provide relevant documents to the EC during the review period. The clinical study must follow the *Declaration of Helsinki* (2013 Edition), the GCP guidelines promulgated by the NMPA and applicable regulatory requirements.

Any modification of the clinical study protocol during the research process must be approved by the EC. The investigator is responsible for regularly submitting study progress reports in accordance with the relevant requirements of the EC. After the study ends, a clinical study report should be submitted to the EC for review.

13.2.2. Subjects' Informed Consent

Subjects and/or their guardians must give their informed consent before the subjects undergoing any operations related to the study in order to protect their legitimate rights and interests. The investigator is responsible for fully and completely introducing the study objectives, methods, effects of the study drug, reasonable expected benefits, possible adverse reactions, and possible study risks to the subjects and/or their guardians. Subjects and/or their guardians should be informed of rights, risks, and benefits of the subjects, and any new information about the study drug should be notified thereto in a timely manner. Subjects and/or their guardians should be informed that the clinical study is completely based on the principle of voluntary participation. Subjects can unconditionally withdraw from the study at any time during the trial and will not be punished for withdrawing from the study. Subjects and/or their guardians should be informed that the investigator and the sponsor have the right to read, store, and statistically analyze the data of subjects in the study in accordance with relevant regulations. The version of the ICF and the date of writing or revision should be indicated. Only subjects who fully understand the risks and benefits of the clinical study, as well as potential AEs, and sign and date on the ICF can participate in the clinical study. If the clinical study protocol is

modified to a certain extent during the research process, the ICF may be modified according to the revised content. After the revised ICF is approved by the EC, an updated ICF re-signed by the subjects and/or their guardians must be obtained.

13.2.3. Clinical Study Protocol Changes and Protocol Modifications

The modifications of the study protocol must be communicated with the study site in written form. The investigator is responsible for obtaining the EC approval for all protocol modifications and forwarding a copy of the approval to the sponsor. The investigator shall not implement this study in accordance with the study protocol amendment before it is approved by the EC.

13.3. Verification of Original Records

The investigator must properly handle all data obtained in the course of the clinical study to ensure the rights and privacy of subjects participating in the clinical study. The investigator must agree that the monitor/auditor/inspector can access and review the required clinical research data in order to verify the accuracy of the original materials and understand the progress of the study. If the original record cannot be verified, the investigator should agree to assist the monitor/auditor/inspector to further confirm the quality control of the data.

13.4. Quality Assurance and Review

All drugs and materials used in the clinical study must be based on quality control. The sponsor and its authorized personnel or related medical management agencies have the right to review the clinical study, the purpose of which is to ensure the authenticity of the clinical study record data and to comply with the provisions of the clinical study protocol.

This study will be organized, carried out and reported in accordance with the protocol and the standard operating procedures of the sponsor and CRO. In ICH E6, quality assurance (QA) is defined as “all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)”. The sponsor's QA work will be carried out in accordance with the regulations of the study audit plan. Section 5.19.3 (b) of ICH E6 stipulates that the audit plan and procedures for a trial audit should be guided by the importance of the trial to submission to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s). The QA work can be outsourced to a CRO or an independent consulting agency. The investigator is required to support the audit work, attend the audit action as required by the auditor, and allow the auditor to directly access the original data/documents, including all medical records, study-related documents and letters, and the informed consent documents of the clinical trial. Clinical study subjects will be informed of the inspection or audit process of the clinical study, but the privacy and data of subjects will be strictly protected.

13.5. Electronic Case Report Form

CRO database programmers will establish eCRF in the EDC system. The eCRF only uses appropriate identification codes (e.g., study site number and subject number) to identify different subjects. eCRF is used to record the clinical research data of subjects and is an integral part of the study and related study reports, so the entry must be accurate and complete. The investigator or the site staff authorized by the investigator is responsible for entering, correcting or modifying the subject data in the EDC system. It must be ensured that all data is entered and stored. The investigator must declare that all the information in the eCRF is true through an electronic signature.

All data should be entered into the EDC during the visit or as soon as possible after the visit in order to record the subject's condition. The eCRF must be kept up-to-date to ensure that it reflects the latest dynamics of the subjects.

The sponsor or the CRA designated by the CRO will regularly monitor the eCRF of the study site, and check the data recorded in the eCRF with the source files and source data to ensure the completeness and accuracy of the data. Manual queries will be proposed in the EDC system for questions about data omissions, modifications or clarifications.

13.6. Drug Counting

The sponsor is responsible for the supply of study drugs. After receiving the study drug, the investigator or authorized personnel must sign for receipt after verifying that it is correct, and store it in accordance with the specified storage conditions.

The investigator or authorized relevant personnel is responsible for accurately recording and keeping records of the distribution or use of study drugs by subjects. The study site must keep all used and unused study drugs in the original packaging for the sponsor or CRO company personnel to monitor. At the end of the study, all used and unused drugs and packaging boxes should be returned to the sponsor.

13.7. Study Monitoring

The sponsor will entrust the CRO to conduct research and monitoring work. The CRA appointed by the CRO should be familiar with the relevant knowledge of the investigational medicinal product, familiar with the trial protocol, informed consent form and other written materials provided to the subjects, and familiar with the clinical trial standard operating procedures, GCP and other related regulations. Monitors should earnestly perform their monitoring duties in accordance with the requirements of the sponsor to ensure that the clinical trial is correctly implemented and recorded in accordance with the trial protocol.

Before the start of the study, the sponsor or the CRA appointed by the CRO should inspect the clinical study site to confirm that the investigator has sufficient qualifications and resources to complete the trial, that the clinical trial institution has the appropriate conditions to complete the trial, including staffing and training, and that the laboratory is well-equipped and well-

functioning, and has various inspection conditions related to the trial.

The CRA appointed by the CRO will regularly conduct on-site monitoring of the study site, and the visit date of each monitoring needs to be recorded on the site visit record of the study site.

The CRA's study monitoring activities include:

- Verify that the investigational medicinal product is within the validity period, the storage conditions are acceptable, and the supply is sufficient during the clinical trial; the investigational medicinal product is only provided to appropriate subjects in accordance with the dose specified in the trial protocol; the subject receives the instructions for correct use, handling, storage and return of the investigational medicinal product; the clinical trial institution has proper control and records for receiving, using, and returning the investigational medicinal product; the clinical trial institution's disposal of unused investigational medicinal products meets relevant laws and regulations and the requirements of the sponsor.
- Verify the investigator's implementation of the trial protocol during the implementation of the clinical trial; confirm that all subjects or their guardians have signed the informed consent form before the trial; ensure that the investigator receives the latest version of the Investigator's Brochure, all trial-related documents and required supplies for the trial, and implement in accordance with the requirements of relevant laws and regulations; ensure that the study staff has a full understanding of the clinical trial.
- Verify that the study staff performs the duties stipulated in the trial protocol and contract, and whether these duties are delegated to unauthorized personnel; confirm that the selected subjects are qualified and report the enrollment rate and the progress of the clinical trial; confirm that the record and the report are correct and complete, the trial records and files are updated in real time and kept intact; verify that all medical reports, records and files provided by the investigator are traceable, clear, synchronized, original, accurate and complete, with the date and trial number specified.
- Verify the accuracy and completeness of the eCRF entry and compare it with the source files. The monitor should pay attention and verify that the data specified in the trial protocol is accurately recorded in the eCRF and consistent with the source files; confirm the subject's dose changes, treatment changes, adverse events, concomitant medications, complications, loss to follow-up, and omissions in examinations are all recorded in the eCRF; confirm that the follow-up not performed, tests not implemented and examinations not performed by the investigator, and whether mistakes and omissions have been corrected are all recorded in the eCRF; verify that the withdrawal and loss to follow-up of selected subjects have been recorded and explained in the eCRF.

- The investigator should be notified of errors, omissions or unclear writing of eCRF; the monitor should confirm that the corrections, additions, or deletions made are operated by the investigator or authorized personnel, and have been signed and dated by the modifier. If necessary, the reason for the modification should be explained.
- Confirm that AEs have been reported within the specified time limit in accordance with relevant laws and regulations, the trial protocol, and the requirements of the EC and the sponsor.
- Confirm whether the investigator has saved the necessary documents in accordance with the
- In the event of deviations from the trial protocol, standard operating procedures, and relevant laws and regulations, it is necessary to communicate with the investigator in a timely manner, and appropriate measures should be taken to prevent recurrence.
- The sponsor authorizes the monitor to have the right to verify; all observations and discoveries during the audit must be able to be verified. If the electronic records are kept in the research base, the method of verification must be discussed with the study members.

  The source files must at least be used to verify:
  - The identity of the subject and whether he/she is qualified;
  - Appropriate informed consent procedures;
  - Visit date;
  - Records of safety and efficacy parameters;
  - Adequate AE reports and visits;
  - Treatment with concomitant medication;
  - Receipt/distribution/return records of drugs;
  - Study drug administration information;
  - The subject’s completion of the treatment, termination of the treatment or withdrawal from the study, and the appropriate reason;
  - The data is true, accurate and complete;
  - The safety and rights of subjects are protected;
  - The investigator's implementation complies with the currently approved protocol, GCP and all relevant regulatory requirements.

The objectives that need to be achieved during the monitoring include:

- Check and evaluate the study progress
- Review the collected research data
- Implement source file verification process
- Identify any problems and develop solutions

After each monitoring, the monitor should promptly report in writing to the sponsor and/or the CRO entrusted by the sponsor; the report should include the date and location of the monitoring,

the name of the monitor, and the name of the investigator and other personnel contacted by the monitor; the report should also include the summary of the monitoring work, a description of the problems and facts found in the clinical trial, deviations and defects from the trial protocol, and the monitoring conclusion; the report should state corrective actions that have been adopted or are to be adopted in response to the problems found in the monitoring, and recommendations to ensure that the trial is implemented in compliance with the trial protocol; the report should provide sufficient details to verify compliance with the monitoring plan. The centralized monitoring report can be submitted separately from the on-site monitoring report. The sponsor should review and follow up on the problems in the monitoring report, and keep them in the form of a document.

During the study period, the CRA needs to directly consult the source data and source files related to the clinical trial with the consent of the investigator and the clinical trial institution. The investigator must ensure that he/she and related study staff regularly meet with the monitor to discuss the findings during the visit and any related issues. In addition, the investigator and the clinical trial institution will allow auditors, EC reviewers and inspectors of the drug regulatory authority to directly access source data and source files related to the clinical trial.

The investigator will also allow sponsor representatives, NMPA and/or relevant health authorities to inspect the facilities and records related to the study.

The medical information of the subjects obtained during the research process is confidential, and disclosure to third parties other than the above is prohibited.

13.8. Protocol Deviations

The investigator should perform this clinical trial in accordance with the clinical trial protocol approved by the EC and follow the GCP regulations. The protocol is designed to enable the investigator to follow the provisions of Section 4 of ICH E6. During the trial, the investigator shall not deviate from the protocol unless emergency measures are required to eliminate the direct harm to the subjects. When there are other unexpected situations that require deviation from the procedures specified in the protocol, the investigator should consult with the medical monitor (and the EC, if necessary) to determine appropriate measures.

The study site should record all protocol deviations, including but not limited to the time when the protocol deviation occurs, the time of discovery, the description of the event and the measures taken. In the event of serious protocol deviations, the study site should promptly notify the medical monitor, CRA, and EC.

13.9. Study Completion

After the study is completed and/or terminated, the sponsor or the CRO requires the provision of the following data and materials:

- All case report forms correctly completed by the study staff and signed by the investigator;

- All laboratory results, clinical data and specific test results obtained from the study screening to the end of the follow-up period;
- Printed results of pathological diagnosis and assessment of original materials during the study period;
- Completed drug inventory records and study materials return records.

13.10. Intellectual Property Rights

All information obtained from the sponsor falls into the intellectual property rights of the sponsor. Therefore, the clinical trial investigator and all other relevant personnel must strictly keep it confidential, and shall not disclose it to any third party without the prior consent of the trial sponsor.

13.11. Subject Privacy

The investigator must ensure the privacy of clinical study subjects. In all documents submitted to the sponsor, only the subjects' number and initials are used to identify the clinical study subjects, and the subjects' full names cannot be displayed. The investigator must properly keep the subjects' names, addresses and corresponding registration forms. These registration forms are to be kept strictly confidential by the investigator and cannot be submitted to the sponsor.

14. Paper Publication

The sponsor has exclusive rights to this study. Because there are many study sites participating in this study, unless approved by the sponsor, individual sites or investigators are not allowed to write and publish personal articles until the final report of the multi-center study is completed. Regarding the manuscript and publication, the sponsor has the right of final decision.

15. Data Archiving

15.1. Source Data and Source Files

In this trial, the source data includes clinical findings, observations, and records of other related activities required to reconstruct and evaluate the clinical trial. The original data is contained in the source files.

The source files involved in the clinical study are original records, documents and data (such as hospital medical records, medical images, laboratory records, memos, subject diaries or assessment forms, drug distribution records, data automatically recorded by instruments, microfilms, photographic plates, magnetic media, X-rays, subject files, clinical trial-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies, etc.). Source files must be preserved to support the information provided in the eCRF.

15.2. Materials Preservation of Study Facilities

15.2.1. Materials Related to the Ethics Committee

The personnel in charge of materials preservation in the study facility must keep the EC meeting minutes and abstracts until 5 years after the trial is suspended or completed. If the sponsor wishes to keep them for a longer period of time, both parties will discuss and decide on the retention time and method. If the study facility makes any changes to the file preservation, the personnel in charge of materials preservation or the investigator should contact the sponsor.

15.2.2. Materials Related to the Trial Implementation

The personnel in charge of materials preservation in the study facility must keep the following files until 5 years after the investigational drug is approved for marketing. If the sponsor wishes to keep them for a longer period of time, both parties will discuss and decide on the retention time and method. If the study facility makes any changes to the file preservation, the personnel in charge of materials preservation or the investigator should contact the sponsor.

- Original files;
- The original or copy of the trial contract and informed consent form, and other GCP-related materials provided by the staff of the study facility;
- Trial protocol, GCP-related data obtained from the EC, or other GCP-related materials obtained;
- Records of investigational medicinal product management and other records related to trial implementation.

15.3. Sponsor’s Materials Preservation

The sponsor will keep the following materials (including files and data) until 5 years after the

investigational drug is approved for marketing. According to relevant regulations, a longer term of preservation may be required. It is the responsibility of the sponsor to inform the investigator/study facility when it is no longer necessary to preserve such materials.

- The original or copy of the trial protocol, trial contract and study report, and GCP-related materials provided by the sponsor;
- Case report forms, GCP-related notices, or GCP-related materials obtained from the investigator;
- Monitoring and audit-related records, or other related operation records;
- Data obtained in the trial;
- Relevant records required by the GCP.

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17. Appendices

17.1. Appendix A (Peak Pruritus NRS)

Peak Pruritus Numerical Rating Scale (PP-NRS)

Site No.: Date:

Subject initials: Subject No.:

Visit: Score:

The score ranges from 0 to 10, in which 0 represents “no pruritus” and 10 “worst imaginable pruritus”. How do you rate your most severe puritus in the past 24 hours?

□	□	□	□	□	□	□	□	□	□	□
0	1	2	3	4	5	6	7	8	9	10
No pruritus										Worst imaginable pruritus

17.2. Appendix B (DLQI)

Dermatology Life Quality Index (DLQI)

Site No.: Date:

Subject initials: Subject No.:

Visit: Score:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

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 **yard?**	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
		Not relevant	☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
		Not relevant	☐
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	☐
		Not relevant	☐
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	☐
	Not relevant	☐
7. Over the last week, has your skin prevented you from **working** or **studying?**	Yes	☐
	No	☐
	Not relevant	☐
If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	☐
	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	☐
	Not relevant	☐
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	☐
	A lot	☐
	A little	☐
	Not at all	☐
	Not relevant	☐
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	☐
	Not relevant	☐

Please check you have answered EVERY question.

Thank you.

DLQI - Instructions for use

The Dermatology Life Quality Index questionnaire is designed for use in adults (patients over the age of 16). It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes.

The scoring of each question is as follows:

- Very much scored 3
- A lot scored 2

- A little scored 1
- Not at all scored 0
- Not relevant scored 0
- Question 7: “prevented work or studying” scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Meaning of DLQI Scores

- 0-1 no effect at all on patient's life
- 2-5 small effect on patient's life
- 6-10 moderate effect on patient's life
- 11-20 very large effect on patient's life
- 21-30 extremely large effect on patient's life

17.3. Appendix C (POEM)

Patient Oriented Eczema Measure (POEM)

Site No.: Date:

Subject initials: Subject No.:

Visit: Score:

Please circle one response for each of the seven questions below about your/your child’s eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your/your child’s skin been itchy because of the eczema?**

0 days 1-2 days 3-4 days 5-6 days Every day

2. **Over the last week, on how many nights has your/your child’s sleep been disturbed because of the eczema?**

0 days 1-2 days 3-4 days 5-6 days Every day

3. **Over the last week, on how many days has your/your child’s skin been bleeding because of the eczema?**

0 days 1-2 days 3-4 days 5-6 days Every day

4. **Over the last week, on how many days has your/your child’s skin been weeping or oozing clear fluid because of the eczema?**

0 days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your/your child's skin been cracked because of the eczema?

0 days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your /your child's skin been flaking off because of the eczema?

0 days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?

0 days 1-2 days 3-4 days 5-6 days Every day

Total (maximum 28)_____

Scores are as follows:

- 0 days=0
- 1-2 days=1
- 3-4 days=2
- 5-6 days=3
- Every day=4

17.4. Appendix D (IGA)

Validated Investigator Global Assessment Scale for Atopic Dermatitis

vIGA-AD™

Instruction:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0-Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1-Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2-Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3-Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4-Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

• Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate"

2. Excoriations should not be considered when assessing disease severity

17.5. Appendix E (EASI)

Eczema Area and Severity Index (EASI)

The EASI score quantifies the severity and extent of AD, as well as the severity of erythema, infiltration, excoriation and lichenification of the four anatomical regions—head and neck, trunk, upper extremities and lower extremities.

The total EASI score ranges from 0 (lowest) to 72 (highest); the higher the score, the higher the severity of AD (more severe).

How to Use EASI

The EASI scoring system uses a **defined process** to grade the **severity of the signs** of eczema and the **extent affected**:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a **score** of **between 0 and 6** based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

To aid in your body region grading you can use the **diagrams** in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

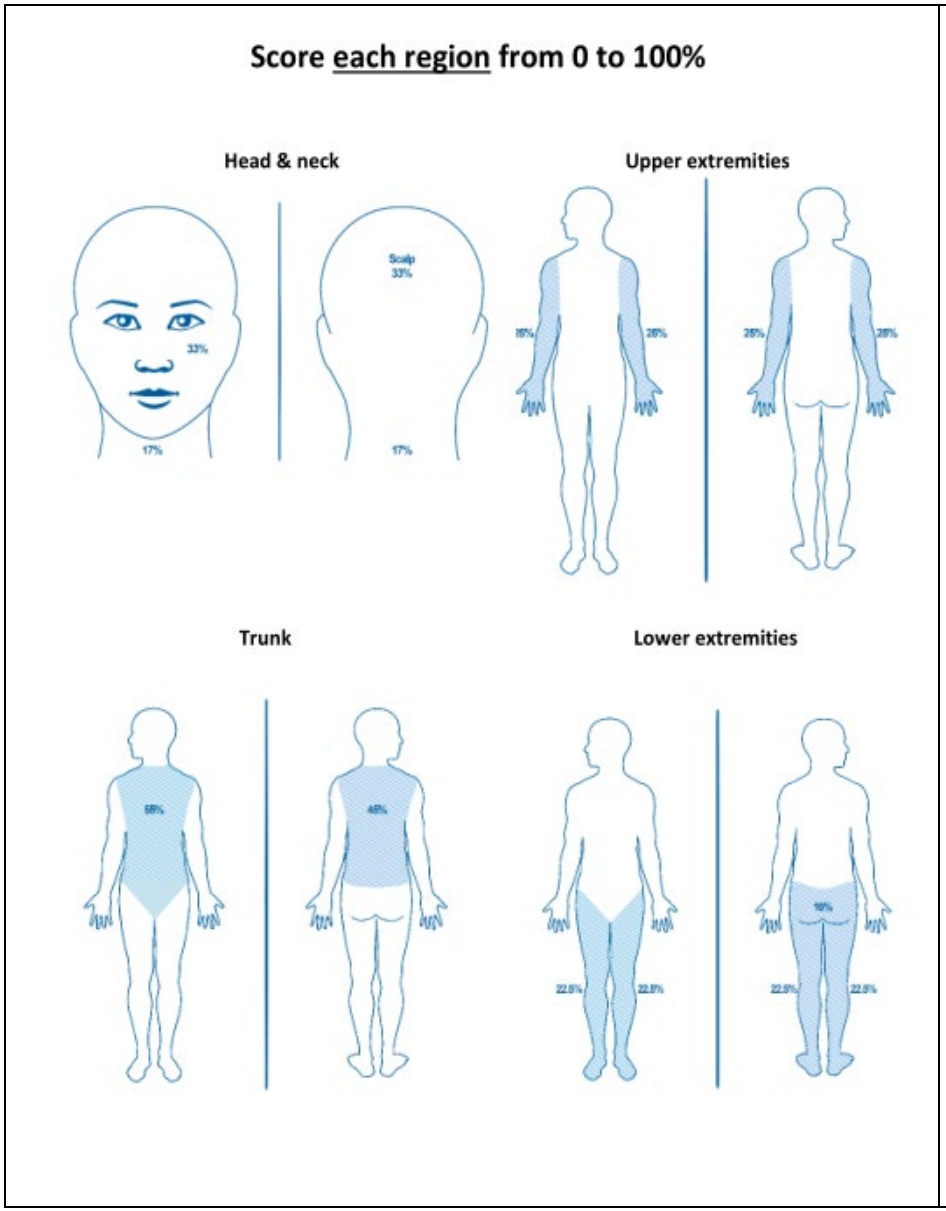
Grade the severity of each sign on a scale of 0 to 3:

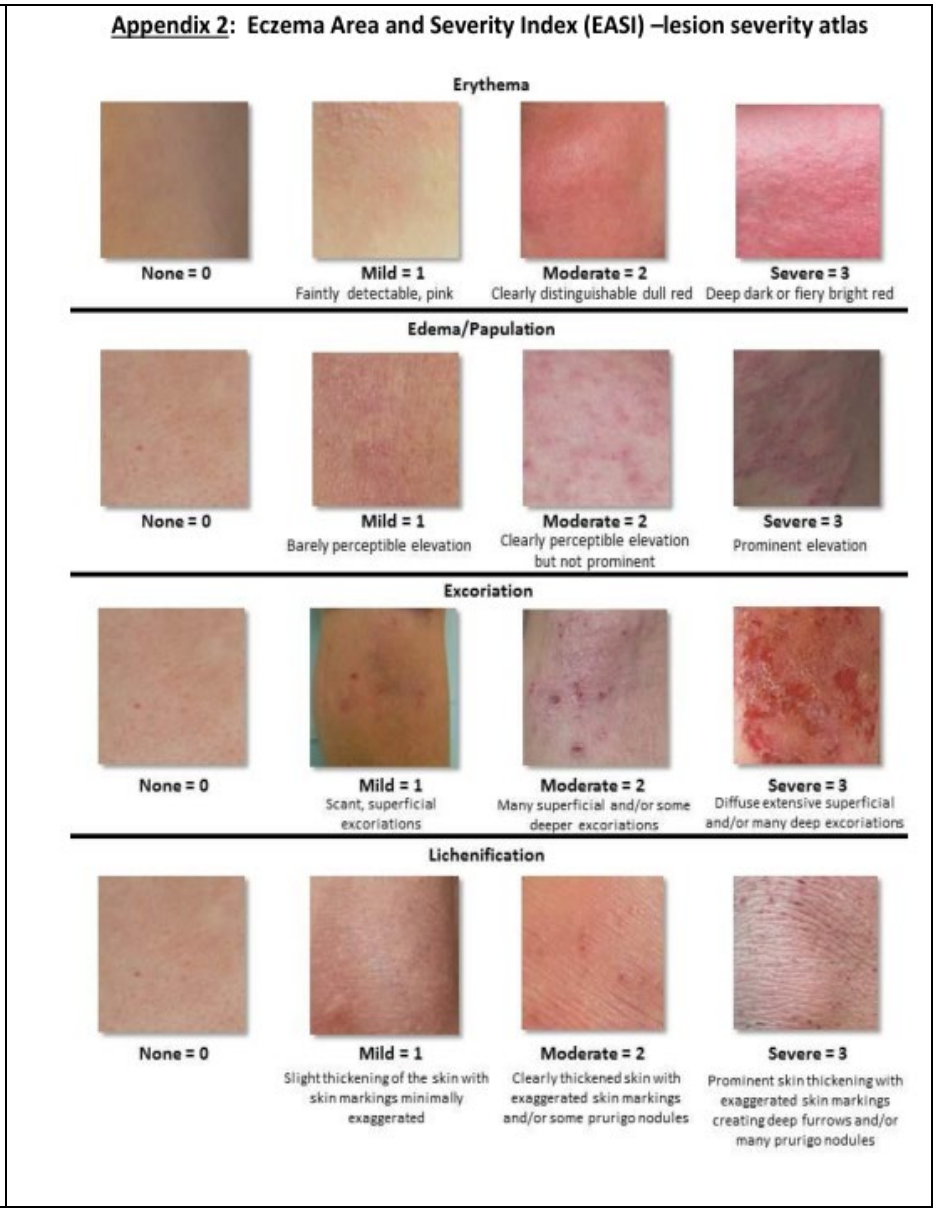
0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a **photographic atlas** of suggested categories is available in **Appendix 2**

Remember: ***Include only inflamed areas*** *in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*


Score each region from 0 to 100%
Head & neck
Upper extremities
Trunk
Lower extremities
Scalp
33%
17%
28%
28%
28%
28%
68%
48%
22.5%
22.5%
19%
22.5%
22.5%


Appendix 2: Eczema Area and Severity Index (EASI) –lesion severity atlas
Erythema
None = 0
Mild = 1
Faintly detectable, pink
Moderate = 2
Clearly distinguishable dull red
Severe = 3
Deep dark or fiery bright red
Edema/Papulation
None = 0
Mild = 1
Barely perceptible elevation
Moderate = 2
Clearly perceptible elevation but not prominent
Severe = 3
Prominent elevation
Excoriation
None = 0
Mild = 1
Scant, superficial excoriations
Moderate = 2
Many superficial and/or some deeper excoriations
Severe = 3
Diffuse extensive superficial and/or many deep excoriations
Lichenification
None = 0
Mild = 1
Slight thickening of the skin with skin markings minimally exaggerated
Moderate = 2
Clearly thickened skin with exaggerated skin markings and/or some prurigo nodules
Severe = 3
Prominent skin thickening with exaggerated skin markings creating deep furrows and/or many prurigo nodules

How to record your scores

The assessed parameters are inserted into a table (example shown below for age≥8 years). The final EASI score ranges from 0-72.

Body region	**Erythema**	**Edema/papulation**	**Excoriation**	**Lichenification**	**Area score**	**Multiplier**	**Score**
Head/neck	**(** +	+	+	**)**	×	× **0.1**	
Trunk	**(** +	+	+	**)**	×	× **0.3**	
Upper extremities	**(** +	+	+	**)**	×	× **0.2**	
Lower extremities	**(** +	+	+	**)**	×	× **0.4**	
The final EASI score is the sum of the 4 region scores							_____ **(0-72)**

Two forms of the EASI scoring system are available depending on the age of the patients. The multipliers for the region score are different in the under 8's version to reflect the relative proportion of body regions in young children.

What is the difference between edema/papulation and lichenification? Consider edema/papulation as corresponding to the acute signs of atopic dermatitis that reflect histological spongiosis. Lichenification are more firm thickened plaques with accentuation of the skin markings that develop as a result of prolonged scratching or rubbing in chronic disease. In darker skin types, follicular lichenification may present as firm flat-topped discrete papules. Grade these chronic lesions as lichenification. **How do I grade prurigo nodules?** Prurigo nodules are larger, deeper lesions as a result of chronic scratching and are graded as areas of lichenification. **How do I grade erythema in darker skin?** To avoid underestimating inflammation in patients with darker skin tones, take into account the underlying skin pigment when grading erythema. Often this means increasing your erythema grade by one level. **What if most areas in a region are a severity grade of 1, but there are some areas that are a grade 3?** Attempt to average the severity across the involved areas in that region. If these areas are close to equal in size, a score of 2 would be most appropriate. If the majority of involved areas are a grade 1, a score of 1 or 1.5 is more appropriate. Be careful not to score the highest severity in a region but the average one. **How do I grade xerosis (dryness), ichthyosis and hyperlinear palms?** Unless there is active acute or chronic eczema overlying these findings, they are not included in the EASI assessment.	**How precise should my assessment of eczema extent be?** The region scores, which reflect the extent of eczema, were designed and validated as rough estimates of the percentage of involved skin. Each region is given a score ranging from 0 to 6, based on a "ballpark" estimation of extent (see region score table in page 1). If you find it difficult to provide a rough estimate of disease extent, you can use the schematics in Appendix 1 to guide you. More time-consuming methods for evaluating disease extent such as the rule of nines or the 'palm' method are generally unnecessary, as the EASI was designed to be easy. **My patient has responded well to treatment and significantly improved since the last visit. Should I adjust the grading based on the patient's relative improvement?** No. The EASI is a static score, meaning that it is done independently at each time point to reflect current severity. You should grade the EASI per visit regardless of the previous status. Studies have shown that the EASI score has good responsiveness, meaning that overall it is sensitive to change and the improvement will be reflected in the total score. **What do the terms erythema, edema/papulation, excoriation and lichenification mean?** These are key signs of atopic dermatitis. Recognizing and grading them properly requires training on the visual and physical exam consistent with these signs. Generally speaking, erythema is skin redness; edema/papulation refers to an elevation or swelling of the skin (that should be differed from lichenification below); excoriations are scratch marks that have broken the skin surface; and lichenification is a leathery thickening of the skin with exaggerated skin markings.

17.6. Appendix F (BSA)

Percentage of body surface area (BSA) affected by AD

The “Rule of Nines” is used to estimate the maximum percentage in each area:

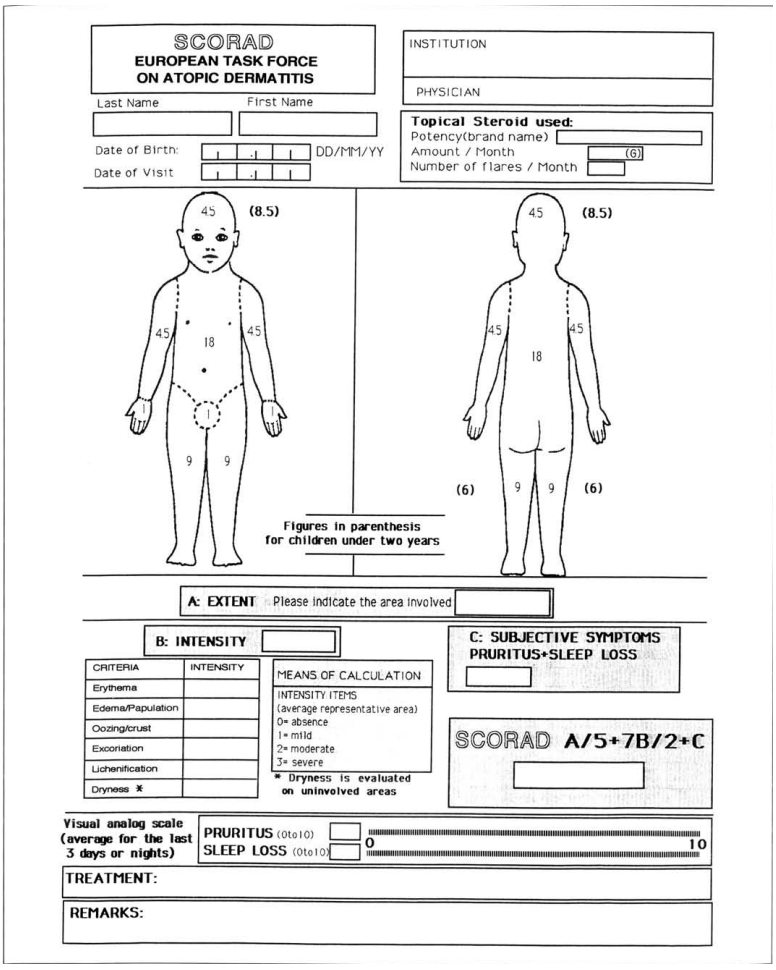
- Head and neck [9%]
- Anterior trunk [18%]
- Back [18%]
- Upper limbs [18%]
- Lower limbs [36%]
- Genitals [1%])

The number of palms of AD-affected skin in a body part can be used to determine the extent (%) of AD involvement in that body part. Regardless of the age of the subject, the area of the subject's entire palm (five fingers adducted together) is about 1% of the subject's BSA. As part of the EASI assessment, the number of palms in different body parts is assessed to calculate the percentage of BSA affected by AD.

17.7. Appendix G (SCORAD)

Scoring Atopic Dermatitis Index (SCORAD)

SCORAD is a clinical tool used to assess the severity of AD (extent/severity) and subjective signs/symptoms (e.g., itch/sleeplessness). The degree of lesions is scored using the "rule of nines" method. The severity is determined by grading the severity of the 6 signs (erythema, edema, oozing/crusting, excoriation, lichenification, and skin dryness) on a 0-3 subscale. The assessment of each sign is scored on the most representative skin lesions. A visual analog scale (VAS) is used to score subjective symptoms, with 0=no itch (or sleeplessness) and 10=most severe itch (or sleeplessness). The total score is the sum of extensiveness/5+7 x severity/2+VAS (symptoms). SCORAD results range from 0 and 103. The higher the score, the more severe the AD.



17.8. Appendix H (Injection Site Assessment)

Injection Site Assessment

Parameter	Grade	Description
Erythema	0	No
	1	Very slight (hardly visible)
	2	Slight (clear boundary)
	3	Moderate
	4	Severe (beet red) to slight eschar formation (deep damage)
Oozing	0	No
	1	Serous
	2	Bloody serous
	3	Bloody
	4	Suppuration
Edema	0	No
	1	Very slight (hardly visible)
	2	Slight (clear boundary)
	3	Moderate (elevated by approximately 1mm)
	4	Severe (elevated by > 1mm and beyond the exposed area)
Induration	0	No
	1	Very mild
	2	Mild (sponge tissue)
	3	Moderate (hard, warm)
	4	Severe (hard, red, hot, crepitus)
Hematoma	0	No
	1	Very mild
	2	Mild
	3	Moderate
	4	Severe