Suzhou Connect Biopharmaceuticals, Ltd.

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

CBP-201-CN002

Statistical Analysis Plan

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Abbreviation

Abbreviation	Explanation
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
CTCAE	Common Terminology Criteria for Adverse Event
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
EOT	End of Treatment
FAS	Full Analysis Set
IGA	Validated Investigator Global Assessment
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
Q1	25% Quartile
Q2W	Once Every 2 Weeks
Q3	75% Quartile
Q4W	Once Every 4 Weeks
RS	Randomization Set
SAE	Serious Adverse Event
SE	Standard Error
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

1. Introduction

This statistical analysis plan (SAP) describes the detailed statistical analysis methods planned for the protocol entitled "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) sponsored by Suzhou Connect Biopharmaceuticals, Ltd.

This plan is prepared based on the Study Protocol Version 4.0 dated 01Aug2022 and the Case Report Form (CRF) Version 3.0 dated 27Apr2022.

2. Study Objectives

2.1. Primary Objective

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

2.2. Secondary Objectives

- 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.

3. Study Design

3.1. Overall Design

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. 255 subjects will be randomized in a 2:1 ratio to receive either CBP-201 300 mg Q2W or placebo.

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 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) 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.

Table 1: Dosing Regimen by Group 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 the treatment assignment for Stage 2 maintenance treatment is based on whether a subject achieves a 50% or greater reduction in 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 efficacy assessment will be randomized in a 1:1 ratio into 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.

Table 2: Dosing Regimen by Group 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.

All subjects (including the subjects who prematurely discontinue treatment) will be followed up for 8 weeks after the last dose.

The overall study design is shown in the diagram below:

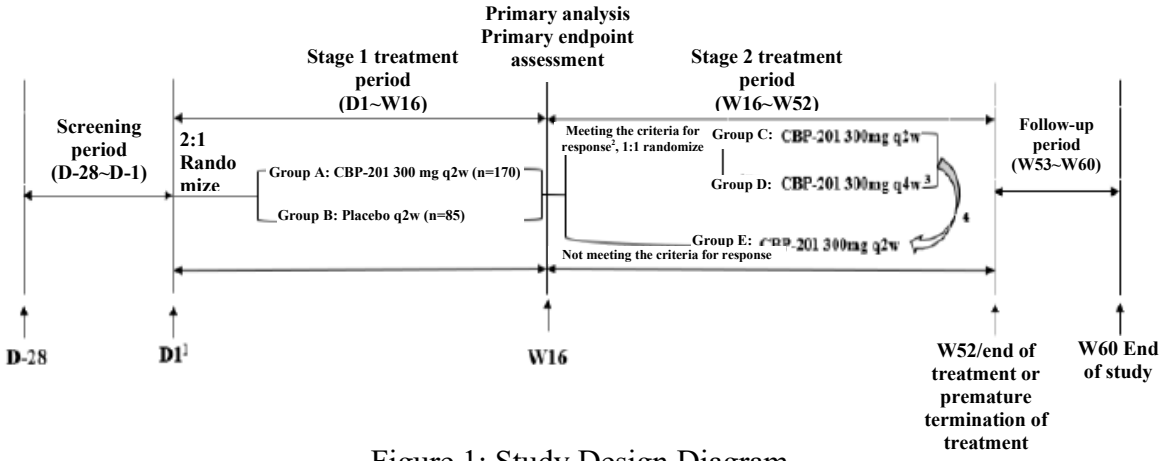

Figure 1: Study Design Diagram

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 greater 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 W50.

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.

3.2. Sample Size

It is planned to enroll 255 subjects (in a 2:1 ratio, 170 subjects in the CBP-201 300 mg Q2W group, and 85 subjects in the placebo group) who will randomly receive either CBP-201 300 mg Q2W or placebo.

This sample size provides a power of approximately more than 90% to detect the difference between groups at a two-sided significance level of 5% under the assumption that 27% and 9% of subjects in the CBP-201 Q2W group and the placebo group can achieve an IGA score of 0-1 at W16 for the primary endpoint, respectively, accounting for a dropout rate of 15%.

Based on the results of another completed phase II international multicenter clinical study of CBP-201 in patients with moderate-to-severe atopic dermatitis, the proportion of subjects achieving the primary efficacy endpoint was 28.1% in the CBP-201 300 mg Q2W group and 10.7% in the placebo group, at a two-sided significance level of 0.05. 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 difference of 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 and Stage 2 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 (a total of 75 cases) based on the protocol after V2.1 will not be included in the primary analysis and Stage 2 analysis, and only supplementary analysis will be performed.

4. Study Endpoints

4.1. Efficacy Endpoints

4.1.1. Primary endpoint

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

4.1.2. Secondary endpoints

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;

4.1.3. 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;
- Change and percentage change in the EASI score from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- 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 and percentage change in the weekly average PP-NRS from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- Change and percentage change in POEM from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects whose IGA score is decreased by ≥2 points from baseline at W52;
- Change and percentage change in the percentage of BSA of AD involvement from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- Change and percentage change in SCORAD from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- 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 and percentage change in DLQI from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60);
- 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;
- The proportion of subjects who maintain EASI-75 response at W52 to the subjects who achieve EASI-75 at W16;

- The proportion of subjects whose IGA score remains 0-1 at W52 to the subjects whose IGA score is 0-1 at W16;
- The proportion of subjects who achieve EASI-75 at each visit time point of Stage 2 maintenance treatment to the subjects who achieve EASI-50 but not EASI-75 at W16;
- The proportion of subjects achieving EASI-50 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects achieving EASI-75 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects achieving EASI-90 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects achieving EASI-100 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects whose IGA score is 0-1 and decreased by $\geqslant$ 2 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects whose weekly average PP-NRS is decreased by $\geqslant$ 4 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);
- The proportion of subjects whose weekly average PP-NRS is decreased by $\geqslant$ 3 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60);

4.2. Safety Endpoints

4.2.1. Drug exposure and compliance

Study drug exposure duration will be summarized by study stage. The duration will be calculated with the following formula:

Exposure duration = date of the last dose - date of the first dose + 14

For analysis of study drug exposure dose, total drug exposure dose of subjects will be summarized.

The compliance with the study drug and emollients (background treatment) will be calculated respectively. If the compliance is lower than 70% or higher than 130%, it will be determined as poor compliance.

Calculation formula of compliance with study drug: Compliance% = actual dose/planned dose * 100%.

Where the actual dose is the total dose of the drug actually used in Stage 1 or 2, and the planned

dose is the total dose of the drug that should be used in Stage 1 or 2.

Calculation formula of compliance with emollients: Compliance% = number of days of using emollients as required by protocol/total number of days for which emollients should be used * 100%

4.2.2. Adverse events (AEs)

AEs

An adverse event refers to any untoward medical occurrence 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. See Section 10.1 of the protocol for details.

Treatment-emergent adverse event (TEAE)

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. The cut-off date of TEAEs in Stage 1 is immediately before the first dose for Stage 2 or 10 weeks (70 days) after end of dosing in Stage 1, whichever occurs first; for the subjects who discontinue administration in Stage 1, the cut-off date of TEAEs is the end of follow-up period. TEAEs in Stage 2 is from the end of the first dose for Stage 2 to the end of the follow-up period.

Drug-related AEs

A drug-related AE refers to an AE whose relationship with the drug is related, possibly related or indeterminable.

The criteria for determination of the correlation of AEs with treatment are as follows:

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 preexisting 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 preexisting 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 preexisting 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 preexisting 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.

Serious Adverse Event (SAE)

An event will be considered an SAE if the following situations occur. See Section 10.1.2 of the protocol for definition of SAE. SAEs will be judged by investigators on CRF.

- 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 (i.e., 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.

Adverse Event of Special Interest (AESI)

AESIs in the study include: Conjunctivitis, keratitis, anaphylactic reaction, injection site reactions which persist over 24 h, AST/ALT increased > 5 × ULN, parasitic and opportunistic infection, pregnancy and symptomatic overdoses.

AEs leading to treatment discontinuation

In the study, action taken with study drug is drug discontinued or the subject will be withdrawn from treatment in response to these AEs.

4.2.3. Laboratory tests

Laboratory tests: Including hematology, blood biochemistry and urinalysis. The specific assessments are shown in Table as follows:

Table 3: 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	

4.2.4. Electrocardiogram (ECG)

12-lead ECG will be performed to collect ventricular rhythm, PR, QRS, QT, and QTcF.

4.2.5. Others

Vital signs

Vital signs include systolic and diastolic blood pressure, heart rate, body temperature, and respiratory rate.

Physical examination

Physical examination includes 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.

Other tests

ADA test.

4.3. PK/PD Endpoints

PK endpoints: To analyze the blood concentration of CBP-201, and calculate the PK characteristics at 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.

5. Statistical Hypothesis

The primary efficacy endpoint of the study is the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16. The following null and alternative hypotheses will be evaluated by statistical tests based on the efficacy endpoint. A two-sided significance level of 5% ($\alpha = 0.05$) will be adopted. If p value is ≤ 0.05, the null hypothesis will be rejected and it is considered that there is a statistically significant difference in IGA parameter between the CBP-201 300 mg Q2W group and the placebo group.

Null hypothesis (H0): Efficacy in the CBP-201 300 mg Q2W group = efficacy in the placebo group

Alternative hypothesis (H1): Efficacy in the CBP-201 300 mg Q2W group ≠ efficacy in the placebo group

6. Analysis Datasets

The primary analysis of the study will be performed based on the data of Stage 1, that is, placebo-controlled stage. The data of primary analysis will include all Stage 1 data from the 255 subjects who are enrolled in accordance with V2.1 and its earlier versions of the protocol. After the 255 subjects enrolled based on the V2.1 and its earlier versions of the protocol complete the 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.

The analyses for Stage 2 will still be based on the data from 255 subjects who are enrolled in accordance with V2.1 and its earlier versions of the protocol. The data analyzed for Stage 2 will include all data from the 255 subjects who are enrolled in accordance with V2.1 and its earlier versions of the protocol that are collected from the start of Stage 2 to the end of study. After all subjects who enter Stage 2 (including the 75 subjects newly enrolled) have completed treatment, evaluation and follow-up, the analyses for Stage 2 will be performed based on the data from 255 subjects who are enrolled in accordance with V2.1 and its earlier versions of the protocol.

Supplementary analysis will include all subjects (including the 75 subjects newly enrolled). The same analysis method as that for the primary analysis and Stage 2 analysis will be used.

The following 6 analysis datasets will be included in the primary analysis.

<u>Screening set 1</u>

It will include all subjects who have signed the informed consent form.

<u>Randomization set 1 (RS1)</u>

RS1 will include all subjects who have been randomized at baseline (D1), regardless of whether they have received the study drug.

Full analysis set 1 (FAS1)

FAS1 will include all subjects who have been randomized and received at least one dose of the study drug. Subjects are analyzed within FAS1 according to treatment assigned.

Per protocol set 1 (PPS1)

PPS1 will include all subjects in FAS1 without any major protocol deviation that affects efficacy analysis. Major protocol deviations that affect efficacy analysis have been discussed and determined at the blinded data review meeting for the primary analysis of the study on September 19, 2022, and have been discussed and determined again at the blinded data review meeting for the final analysis of the study on October 18, 2023. Minutes of the data review meeting will be presented in an annex.

By far, protocol deviations that affect efficacy analysis of the 255 subjects in Stage 1 are due to the following causes:

1. Missing doses (I. Missing W12 and W14 doses; II. Missing 3 doses in Stage 1, equivalent to a compliance with study drug lower than 70%);
2. Missing key efficacy results at W16 (both IGA and EASI missing);
3. Key efficacy results at W16 out of window (both IGA and EASI out of window >10 days);
4. Incorrect stratified randomization (only Stage 1);
5. Violation of inclusion or exclusion criteria (topical corticosteroids are used before baseline; baseline disease severity fails to meet the requirements);
6. Prohibited drugs (non-rescue treatment) that may affect efficacy

Safety set 1 (SS1)

SS1 will include all randomized subjects who have received at least one dose of study drug. Subjects are analyzed within SS1 according to the treatment they actually received.

PK set 1 (PKS1)

PKS1 will include subjects who have received at least one dose of CBP-201 active drug and had at least 1 collected and analyzable PK sample.

The Stage 2 analysis will be defined as the following analysis populations.

Randomization set 2 (RS2)

RS2 will include all subjects who have been randomized to Group C or D and all subjects assigned to Group E.

RS2_R: RS2_R will include all subjects who have been randomized to Group C or D.

RS2_NR: RS2_NR will include all subjects who have been assigned to Group E.

Full analysis set 2 (FAS2)

FAS2 will include all subjects who have been randomized to Group C or D and all subjects who have been assigned to Group E and received at least one dose of the study drug in Stage 2. Subjects are analyzed within FAS2 according to treatment assigned.

FAS2_R: FAS2_R will include all subjects who have been randomized to Group C or D and received at least one dose of the study drug for Stage 2.

FAS2_NR: FAS2_NR will include all subjects who have been assigned to Group E and received at least one dose of the study drug for Stage 2.

Safety set 2 (SS2)

SS2 will include all subjects in RS2 who have received at least one dose of the study drug for Stage 2. Subjects are analyzed within SS2 according to the treatment they actually received.

Safety set 3 (SS3)

SS3 will include all subjects in SS1 and SS2 who have received at least one dose of the study drug.

PK set 2 (PKS2)

PKS2 will include all subjects who have received at least one dose of CBP-201 active drug for Stage 2 and have at least 1 collected and analyzable PK sample for Stage 2.

For the supplementary analysis based on all subjects (including the 75 subjects newly enrolled), the definitions of analysis sets are the same as above.

Table 4: Analysis Population, Treatment Group and Analysis Stage

Analysis Populations	Treatment Groups	Analysis Stage
RS1/ FAS1/ PPS1/ SS1	1) Placebo 2) CBP-201 300 mg Q2W	Stage 1 treatment period.
RS2_R/ FAS2_R	1) Placebo/CBP-201 300 mg Q2W 2) Placebo/CBP-201 300 mg Q4W 3) CBP-201 300 mg Q2W/CBP-201 300 mg Q2W 4) CBP-201 300 mg Q2W/CBP-201 300 mg Q4W 5) Q2W Total 6) Q4W Total 7) Total	From the completion of Stage 2 randomization to the end of study for subjects who have completed Stage 1 and been randomized to Group C or D.
RS2_NR/ FAS2_NR	1) Placebo/CBP-201 300 mg Q2W 2) CBP-201 300 mg Q2W/CBP-201 300 mg Q2W 3) Open-Label Q2W Total	From the start of Stage 2 to the end of study for subjects who have completed Stage 1 and been assigned to Group E.
SS2	1) CBP-201 300 mg Q2W（Group C） 2) CBP-201 300 mg Q4W（Group D）	From the first dose for Stage 2 to the end of Stage 2.

	3) CBP-201 300 mg Q2W（Group E） 4) Total	
SS3	1) CBP-201 300 mg Q2W 2) CBP-201 300 mg Q2W/CBP-201 300 mg Q4W 3) CBP-201 300 mg Q2W/CBP-201 300 mg Q4W/CBP-201 300 mg Q2W 4) CBP-201 300 mg Q4W 5) CBP-201 300 mg Q4W/CBP-201 300 mg Q2W 6) Total	It includes all subjects who have received at least one dose of CBP-201 from Stage 1 to Stage 2. From the first dose of CBP-201 to the end of study.

7. Statistical Methods

7.1. Overall Statistical Consideration

In the statistical tabulations, screening number of subjects is the universal unique identifier of subjects in the study.

General rules of descriptive statistics: Quantitative variables are described by mean, standard deviation, median, minimum, maximum, Q1 and Q3. In terms of rounding, the numbers of decimal places of the minimum and maximum are consistent with that of original value, while those of mean, medium, Q1, and Q3 are 1 more than that of the original value, and that of standard deviation is 2 more than that of the original value. Categorical variables are described by number and percentage of each category. The number of subjects is rounded to integer and percentage is rounded to one decimal place. It is unnecessary to present a percentage when the count is 0.

General rules of inferential statistics: Two-sided test is adopted for all statistical tests (unless otherwise specified). $P<0.05$ will be considered statistically significant (unless otherwise specified). P value is rounded to 4 decimal places. If $P < 0.0001$, it is presented as '< .0001'; if $P > 0.9999$, it is presented as '> .9999'.

For 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.

For the analysis in Stage 2, one group of baselines is defined for efficacy analysis and two groups of baselines are defined for safety analysis. The baseline of efficacy analysis is defined as the last available value before randomization in Stage 1. The baseline of safety analysis in Group 1 is defined as the last available value before the first dose. The baseline of safety analysis in Group 2 is defined as the last available value before the first dose in Stage 2. Efficacy analysis will be performed using the baseline of Group 1. Safety analysis will be performed to analyze the changes from baseline in laboratory test, ECG and vital signs at each visit using the baseline of Group 1 and the baseline of Group 2, respectively.

Statistical analyses will be performed using SAS 9.4.

7.2. Methods for Data Processing

7.2.1. Convention of data processing and processing of missing data

The missing dates of AEs or concomitant medications/treatments will be imputed as follows. The imputation of missing dates will be used for classification only. When tabulations of relevant data are generated, unimputed dates will be still presented.

Missing of start date:

1) If the year and month are known and both are earlier than those of the first dose of the investigational product, the last day of the known month will be used for imputation.
2) If the year and month are known and same as those of the first dose of the investigational product, the start date is the date of the first dose of the investigational product (date refers to “month, day”).
3) If the year and month are known and later than those of the first dose of the investigational product, it will be imputed with the first day of the known month.
4) If only the year is known and earlier than that of the first dose of the investigational product, “December 31” will be used for imputation.
5) If only the year is known and same as that of the first dose of the investigational product, the start date is the date of the first dose of the investigational product (date refers to “month, day”).
6) If only the year is known and later than that of the first dose of the investigational product, it will be imputed with “January 1”.
7) In other situations, the date of the first dose of the investigational product will be taken as corresponding start date.

Missing of end date:

1) If the year and month are known, it will be imputed with the last day of the known month.
2) If only the year is known, it will be imputed with “December 31”.
3) If the end date imputed is earlier than the start date, the end date will be taken as corresponding start date.
4) Other conditions are regarded as missing.

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

7.2.2. Derived and transformed data

When the units of data from laboratories of different sites are inconsistent, the data will be converted according to international standard units.

For laboratory data, if the same parameter is measured multiple times on the same day, the average value of multiple measurements will be used as the measurement this day for analysis.

Duration of exposure to drug (day) = date of the last dose - date of the first dose + 14.

7.3. Study Subjects

7.3.1. Subject disposition

Screening and randomization of subjects will be summarized based on Screening Set 1. The number and percentage of subjects will be calculated, and the reasons for screening failure will be presented; in addition, study drug discontinuation and study termination in both stages will be summarized based on RS1 and RS2, respectively, and the number and percentage of subjects will be calculated. Subject disposition will be tabulated.

7.3.2. Protocol deviations

All subjects who have protocol deviations in Stage 1 will be summarized based on RS1, the number and percentage of subjects will be calculated and tabulated. In addition, all subjects with protocol deviations that have occurred from Stage 2 to end of study will be summarized based on RS2, the number and percentage of subjects will be calculated and tabulated.

7.3.3. Analysis datasets

The subjects who are included to SS1, FAS1, and PPS1 will be summarized based on RS1, and the number and percentage of subjects will be calculated.

The subjects who are included into SS2, FAS2, and PPS2 will be summarized based on RS2, and the number and percentage of subjects will be calculated.

SS3 will include all subjects who have received at least one dose of the study drug. The total number of subjects included into SS3 as well as the specific number of subjects in each treatment group (See Table 4. Analysis Population, Treatment Group and Analysis Stage) will be listed.

7.3.4. Demographics and baseline characteristics

The primary analysis will be performed based on RS1, and Stage 2 analysis will be performed based on RS2.

Demographics such as age, gender, body height, body weight, and BMI will be summarized by descriptive statistics. The severity (moderate [IGA = 3] and severe [IGA = 4]) of atopic dermatitis (AD) at baseline will be summarized, and the number of percentage of subjects will be calculated. The baseline EASI/PP-NRS/BSA/SCORAD/POEM/DLQI will be summarized by descriptive statistics. Demographics and baseline characteristics will be tabulated.

7.3.5. Medical history of subjects

The primary analysis will be performed based on RS1, and Stage 2 analysis will be performed based on RS2.

Medical history will be coded based on Medical Dictionary for Regulatory Activities (MedDRA), and the number and percentage of subjects will be summarized by System Organ Class (SOC) and Preferred Term (PT). Medical history of allergic diseases and allergy history will be summarized separately, and the number and percentage of subjects will be calculated. Medical history will be ranked in descending order of total number of subjects by SOC and PT. All medical histories will be tabulated, and medical history of allergic diseases and allergy history will be tabulated separately.

7.3.6. Prior medication, concomitant medication, and prior and concomitant non-drug therapies

The primary analysis will be performed based on RS1. Stage 2 analysis will be performed based on RS2 (only concomitant medications and treatments in Stage 2).

Prior and Concomitant Medications

Prior medication refers to a non-study drug that is started and ended before the first dose of study drug. Concomitant medication refers to a drug that is started at the time of or after the first dose of study drug, or a drug that is started before the first dose of the study drug and continued after the first dose of the study drug.

Prior and concomitant medications will be coded based on World Health Organization Drug Dictionary (WHODrug), and summarized based on ATC Level 2, ATC Level 4 (if the code is missing, it will be analyzed with the code of previous level) and PT. The number and percentage of subjects will be calculated. Prior and concomitant medications will be ranked in descending order of total number of subjects by ATC Level 2, ATC Level 4 and PT. In addition, they will be tabulated.

Prior and Concomitant Non-drug Therapies

Prior non-drug therapy refers to a therapy that is started and ended before the first dose of study drug. Concomitant non-drug therapy refers to a therapy that is started at the time of or after the first dose of study drug, or a therapy that is started before the first dose of the study drug and continued after the first dose of the study drug.

Prior and concomitant non-drug therapies will be coded by MedDRA. Concomitant non-drug therapies will be summarized by PT. The number and percentage of subjects will be calculated. Prior and concomitant non-drug therapies will be ranked in descending order of total number of subjects. They will be tabulated.

Rescue Treatment

Rescue treatments during treatment period of Stages 1 and 2 will be summarized based on ATC Level 2, ATC Level 4 (if the code is missing, it will be analyzed with the code of previous level) and PT. The number and percentage of subjects will be calculated. These rescue treatments will be ranked in descending order of total number of subjects by ATC Level 2, ATC Level 4 and PT. They will be tabulated.

7.4. Efficacy Analysis

Efficacy analysis in Stage 1 will be performed based on FAS1 and PPS1, mainly the FAS1.

In order to control the type I error rate for multiplicity, a fixed-sequence method will be used. First of all, the active treatment group and the placebo group will be compared for the primary efficacy endpoint; when the primary efficacy endpoint reaches statistical significance, the active treatment group and the placebo group will be compared for the key secondary efficacy endpoints according to the sequence specified in the protocol.

Efficacy analysis in Stage 2 will be performed based on FAS2.

7.4.1. Visit window of efficacy analysis

For scheduled visits, the visit window for efficacy analysis will be based on the visit where the original data are collected. For unscheduled visits and premature withdrawal visit, the visit window for efficacy analysis will be based on the visit closest to the reference date (the previous visit when the distance is the same).

7.4.2. Intercurrent events and handling strategies

See table below for intercurrent events and handling strategies of the primary analysis:

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 response)	• 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 response, the above prohibited drugs/treatments have been used before the W16 visit.	Composite strategy	This type of intercurrent event occurs because of poor response, 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	• 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 for the treatment of AD (except	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

Label	Intercurrent event	Strategy	Remarks
negligible impact on the assessment of the primary endpoint)	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.		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 Event 1 due to poor response, with a major 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 for the treatment of AD (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 due to poor response before the W16 visit is more than 7 days, or the end date is less than 4 weeks away from the W16 visit.	Composite strategy	This type of intercurrent event occurs because of poor response, 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 4 (premature discontinuation of treatment/EOT due to AEs)	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 premature discontinuation of treatment/EOT.	Composite strategy	This type of intercurrent event occurs because of poor safety of treatment, 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 (W12 and W14) immediately before the W16 visit is missing or the administration in the Stage 1 treatment period is missing for ≥3 times.	Hypothetical strategy	The observed values are not used, and the J2R (jump to reference) method is used for imputation.
Intercurrent event 6 (use of prohibited	The following prohibited drugs/treatments have been used before the W16 visit not because of the poor response:	Hypothetical strategy	The observed values are not used, and the J2R (jump to

Label	Intercurrent event	Strategy	Remarks
drugs/treatments specified in the protocol not for poor response, with a major impact on the assessment of the primary endpoint)	• 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. Or The cumulative duration of use of the following prohibited drugs/treatments not due to the poor response before the W16 visit is more than 7 days, or the end date is less than 4 weeks away from the W16 visit: • Initiation of SIT, or dose up-regulation; • TCS or TCI (topical drugs can be used for AD lesion areas only); • Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies; • Bleaching baths more than 2 times a week; • Any drug for the treatment of AD (topical drugs can be used for AD lesion areas only) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity.		reference) method is used for imputation.

7.4.3. Analysis of the primary efficacy endpoint and key secondary efficacy 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 primary endpoint	The difference in efficacy in patients aged 12 years and older with moderate to severe AD 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 response, or has premature discontinuation of treatment/EOT due to AEs.	FAS1 (will include all subjects in RS1 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 7.4.2. 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.	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. **Sensitivity analysis 3:** For the subjects who are incorrectly stratified and randomized, the analysis will be performed using the stratification during randomization and the same method as the main estimand; **Supplementary analysis 1:** The analysis will be performed using the same method as the main estimand based on the PPS1. **Supplementary analysis 2:** The treatment policy strategy will be used for all intercurrent events; the FAS1 will be used,

Label of estimand	Description of estimand	Main estimator			Sensitivity/ Supplementary analysis
		Analysis sets	**Rules for imputation**	**Model/method for the main analytical methods**	
					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 test 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;	FAS1 (will include all subjects in RS1 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 7.4.2. 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)	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	**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. **Sensitivity analysis 2:** For the subjects who are incorrectly stratified and randomized, the analysis will be performed using the stratification during randomization and the method the same as the main estimator; **Supplementary analysis 1:** The analysis will be performed using the same method as the main estimand based on the PPS1. **Supplementary analysis 2:** The treatment policy strategy will be used for all intercurrent events; the FAS1 will be used,

Label of estimand	Description of estimand	Main estimator			Sensitivity/ Supplementary analysis
		Analysis sets	Rules for imputation	Model/method for the main analytical methods	
	• Change and percentage change in the weekly 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 response, or has premature discontinuation of treatment/EOT due to AEs. In this case, continuous variables should be imputed with WOCF.		method will be used to impute the missing data in the CBP- 201 group.	corresponding endpoint, visit, interaction of visit and treatment group, and the LSMEAN estimate values and their 95% confidence intervals will be summarized.	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 test group.

In the J2R (jump to reference) method, when the data of subjects of the active treatment group are missing, it is assumed that their statistical results are the same as those of the placebo group, that is, it is considered that the pharmacological action of the drug for the active treatment group is the same as that of the placebo group. PROC MI will be used for J2R imputation, and the missing data of the active treatment group will be imputed with the results obtained by posterior predictive distribution of the placebo group. Markov Chain Monte Carlo (MCMC) will be used to extend the data, and a regression method will be used to generate M datasets (M is set as 30 for the primary analysis and as 1000 for other cases in this study). The imputed variables should include: treatment group, stratification factor (severity of baseline disease), baseline value of corresponding endpoint and measurement at each visit. Random seed is the earliest date of the first dose to all subjects.

Table 5 Random Seeds of Multiple Imputation

Endpoints	Random Seeds
IGA	Minimum date of the first dose
EASI	Minimum date of the first dose + 1
PP-NRS	Minimum date of the first dose + 2
BSA	Minimum date of the first dose + 3
SCORAD	Minimum date of the first dose + 4
DLQI	Minimum date of the first dose + 5
POEM	Minimum date of the first dose + 6

Tipping point analysis: To evaluate the robustness of the primary efficacy endpoint analysis, tipping point analysis should be performed on the primary efficacy endpoint at W16. The tipping point method is binary, that is, the assumptions of missing values of the active treatment group and the placebo group are mutually independent. Assuming that the response rate of missing values of the two groups increases by 10% from 0 to 100%, the subjects with a missing response in the two groups at a certain percentage will be randomly assigned as responders and non-responders in a specified number of imputed datasets randomly generated by the binomial distribution. Then the same analysis method as that for the primary study endpoint will be used to obtain the comparison results between the two groups in each imputed dataset. Finally, Rubin's Rule will be used to pool these results. If there is a pair of assumed response rate that overturns the study conclusion, that is, p value is more than 0.05, the two assumed response rates will be the cut-off points.

Subgroup analysis will be performed on the primary efficacy endpoint (the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16) and the key secondary efficacy endpoint (the proportion of subjects achieving EASI-75 at W16) by gender (male/female), severity of baseline disease (moderate [IGA = 3]/severe [IGA = 4]), history of allergic diseases or allergy history (yes/no), baseline EASI (< baseline median EASI/≥ baseline median EASI), baseline PP-NRS (< baseline median PP-NRS/≥ baseline median PP-NRS). The analytical method is the same as the primary analysis method for the

primary efficacy endpoint and the key secondary efficacy endpoint. The subjects with missing subgroup variables will not be included.

Sensitivity analysis will be performed on the primary efficacy endpoint (the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16) and the key secondary efficacy endpoint (the proportion of subjects achieving EASI-75 at W16) using the stratification during randomization and the method the same as the main estimator.

7.4.4. Other efficacy endpoint analysis

The categorical efficacy endpoint analysis in Stage 1 will be performed using the same method as the primary efficacy endpoint analysis.

The continuous efficacy endpoint analysis in Stage 1 will be performed using the same method as the secondary efficacy endpoint analysis.

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.

The number of AD recurrence, the number of subjects with AD recurrence, and the number of days of AD recurrence in Stage 1, from baseline to W8, from W9 to W16 will be analyzed. The total number of AD recurrence in each stage will be summarized. AD recurrence will be summarized by the number of recurrences, that is, 0, 1, 2 and ≥ 3. The number and percentage of subjects will be calculated. Chi-squared test will be adopted to compare whether the differences between the two groups are statistically significant. The total number of subjects with AD recurrence in each stage will be summarized, and the number and percentage of subjects will be calculated. Chi-squared test will be performed to compare whether the differences between the two groups are statistically significant. The number of days of AD recurrence in each stage will be summarized by descriptive statistics.

7.4.5. Efficacy analysis in stage 2

During efficacy analysis in Stage 2, the percentage of subjects achieving efficacy endpoint and its confidence interval will be calculated for categorical efficacy endpoints. For continuous efficacy endpoints, ANCOVA model will be used to calculate the mean, the Least Square Mean, 95% confidence interval and SE of the change from baseline and percentage change from baseline of each efficacy endpoint. The model will include treatment group, severity of baseline disease (IGA 3 or 4), and baseline value of corresponding endpoint. Inferential statistics will not be performed during the Stage 2 analysis. The following two analyses will be performed.

Analysis method 1: Categorical efficacy endpoints after the occurrence of events will be regarded as no response for subjects who have the following conditions; continuous efficacy endpoints after the occurrence of events will be imputed using WOCF in Stage 2; other missing data except for the conditions above will be imputed using multiple imputation (MI).

- Group adjustment

- Premature discontinuation of treatment/EOT due to AEs
- Use of prohibited drugs/treatments specified in the protocol as a rescue treatment for AD due to poor response, which has a major impact on the assessment of the efficacy endpoints, including:

The following prohibited drugs/treatments are used during Stage 2 (W16 to W52):

- 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.

Or the following prohibited drugs/treatments are used for a cumulative period of more than 7 days during Stage 2 (W16 to W52):

- Initiation of SIT, or dose up-regulation;
- TCS or TCI (topical drugs can be used for AD lesion areas only);
- Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies;
- Bleaching baths more than 2 times a week;
- Any drug for the treatment of AD (If topical drugs, only those used for AD lesion areas will be counted) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity.

Analysis method 2: The analysis will be performed using the actual observed values. If the actual observed value is missing, it will be imputed by MI.

During MI in Stage 2, M data sets will be generated by regression method (M is set as 1000 during Stage 2 analysis).

7.5. Safety Analysis

7.5.1. Drug exposure and compliance

Study drug exposure will be analyzed based on SS1, SS2 and SS3. Study drug exposure duration and exposure dose during treatment period of Stages 1 and 2 will be summarized by descriptive statistics.

The compliance with the study drug and emollients (background treatment) in Stages 1 and 2 will be summarized by descriptive statistics. The subjects with a compliance < 70%, ≥ 70% and ≤ 130%, and > 130% will be summarized, and the number and percentage of subjects will

be calculated. Subjects' compliance with the study drug and emollients (background treatment) will be tabulated.

7.5.2. AEs

AEs will be analyzed based on the SS1 and SS2. Subjects who have received at least one dose of the study drug will be analyzed based on SS3.

AEs will be coded using MedDRA.

The occurrence of overall AEs will be summarized to generate summary tabulations of TEAEs. TEAEs of special interest and drug-related AESIs will be summarized. The numbers of subjects with various AEs, numbers and incidences of events will be calculated. The number of subjects with various AEs, the number of events, the incidence and annual incidence of events will be calculated based on SS3.

AEs, drug-related AEs, SAEs, AESIs, AEs leading to death, AEs leading to treatment discontinuation, injection site AEs, CTCAE grade 3-5 AEs, AEs with an incidence of > 5%, and AD recurrence-related AEs will be tabulated.

The incidences of the following TEAEs will be summarized by SOC and PT, the numbers of subjects with various AEs, and the numbers and incidences of events will be calculated. They will be ranked in descending order of total number of subjects by SOC and PT. In addition, annual incidences of TEAEs, treatment-emergent SAEs, treatment-emergent AESIs, drug-related AEs, drug-related SAEs will be calculated by SOC and PT based on SS3.

1) TEAEs;
2) Drug-related AEs;
3) SAEs;
4) Drug-related SAEs;
5) AEs leading to death;
6) AEs leading to treatment discontinuation;
7) AEs leading to treatment interruption;
8) AESIs;
9) Drug-related AESIs;
10) Injection site AEs;
11) CTCAE grade 3-5 AEs;
12) AEs with an incidence of > 5%;

In addition, the incidences of TEAEs, AESIs, and injection site AEs will be summarized by CTCAE Grade, correlation with study drug, SOC and PT, and the number and percentage of subjects will be calculated.

A subject with an AE of the same SOC and PT more than once will have that event counted only once within each SOC and PT.

7.5.3. Laboratory test results

Analysis will be performed based on SS1, SS2 and SS3. Analysis will not be performed using SS3 by visit.

The hematology, blood biochemistry and urinalysis parameters at baseline and each visit and their changes from baseline at each visit will be summarized by descriptive statistics.

The number and percentage of subjects whose hematology, blood biochemistry and urinalysis parameters at baseline and each visit are below, within and above the normal range will be summarized.

Pre-treatment and post-treatment laboratory test results are classified into abnormal with clinical significance, abnormal without clinical significance, normal, and not tested in an order of abnormal with clinical significance > abnormal without clinical significance > normal > not tested. Then shift tables are generated. The shift tables are generated based on CTCAE 5.0.

All laboratory test results and abnormal laboratory test results for hematology, blood biochemistry, urinalysis and urine pregnancy will be tabulated.

Qualitative laboratory test results will be summarized by visit. The number and percentage of subjects for each category will be calculated and tabulated.

7.5.4. ECG

Analysis will be performed based on SS1, SS2 and SS3. Analysis will not be performed using SS3 by visit.

Ventricular rhythm, PR, QRS, QT and QTcF results at each post-baseline visit and their changes from baseline at each visit will be summarized by descriptive statistics. The analysis of variance will be used to detect possible difference between groups.

Special attention will be paid to QTcF interval prolongation:

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms
- Increase in QTcF interval from baseline > 30 ms
- Increase in QTcF interval from baseline > 60 ms

Pre-treatment and post-treatment ECG results are classified into abnormal with clinical significance, abnormal without clinical significance, normal, and not tested in an order of abnormal with clinical significance > abnormal without clinical significance > normal > not tested. Then shift tables are generated.

ECG results of QTcF interval prolongation will be tabulated. All ECG results and clinically significant abnormal ECG results will be tabulated.

7.5.5. Other safety evaluation

The following analyses will be performed based on SS1, SS2 and SS3. Analysis will not be performed using SS3 by visit.

Physical examination

Physical examination results at each visit in Stages 1 and 2 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All physical examination results and abnormal physical examination results with clinical significance will be tabulated.

Vital signs

The vital signs at baseline and their changes from baseline at each visit of Stages 1 and 2 will be summarized by descriptive statistics. The analysis of variance will be used to detect possible difference between groups.

Vital sign results at each visit of Stages 1 and 2 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All vital sign results and abnormal vital sign results with clinical significance will be tabulated.

Eye examination

Eye examination results at each visit of Stages 1 and 2 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All eye examination results and abnormal eye examination results with clinical significance will be tabulated.

ADA test

See PK/PD statistical analysis plan for details.

7.6. Pharmacokinetics (PK) analysis

See PK/PD statistical analysis plan for details.

7.7. Pharmacodynamics (PD) and Biomarker Analysis

See PK/PD statistical analysis plan for details.

7.8. Changes to Planned Analysis in the Protocol

For the other efficacy endpoints, the following updates will be made:

Description in protocol	Updated description in SAP
The percentage decrease in the overall EASI score between W16 and W52	Change and percentage change in the EASI score from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
Change in weekly average PP-NRS from baseline between W16 and W52	Change and percentage change in the weekly average PP-NRS from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
Change in POEM from baseline between W16 and W52	Change and percentage change in POEM from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
Percentage change in the BSA of AD involvement from baseline between W16 and W52	Change and percentage change in the percentage of BSA of AD involvement from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
Change in SCORAD from baseline between W16 and W52	Change and percentage change in SCORAD from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
Change in DLQI from baseline between W16 and W52	Change and percentage change in DLQI from baseline at each visit time point from the start of Stage 2 maintenance treatment to the end of study (W60)
None	Other new efficacy endpoints: • The proportion of subjects who maintain EASI-75 response at W52 to the subjects who achieve EASI-75 at W16 • The proportion of subjects whose IGA score remains 0-1 at W52 to the subjects whose IGA score is 0-1 at W16 • The proportion of subjects who achieve EASI-75 at each visit time point of Stage 2 maintenance treatment to the subjects who achieve EASI-50 but not EASI-75 at W16 • The proportion of subjects achieving EASI-50 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60) • The proportion of subjects achieving EASI-75 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60) • The proportion of subjects achieving EASI-90 at each of the other visit time points from the start of Stage 2 maintenance

	treatment to the end of study (W60) • The proportion of subjects achieving EASI-100 at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60) • The proportion of subjects whose IGA score is 0-1 and decreased by ⩾ 2 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60) • The proportion of subjects whose weekly average PP-NRS is decreased by ⩾ 4 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60) • The proportion of subjects whose weekly average PP-NRS is decreased by ⩾ 3 points from baseline at each of the other visit time points from the start of Stage 2 maintenance treatment to the end of study (W60)

8. References

Guidelines for Management and Statistical Analysis Plan of Drug Clinical Trial Data 2021.

Suzhou Connect Biopharmaceuticals, Ltd.

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

CBP-201-CN002

Statistical Analysis Plan

NCT Number：NCT05017480

Version: 1.0

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Approval Page of Sponsor

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

CBP-201-CN002

Statistical Analysis Plan

Version: 1.0

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1.0	September 20, 2022	Chen Jingyun	Initial version

Table of Contents

Abbreviation

Abbreviation	Explanation
AD	Atopic Dermatitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
CTCAE	Common Terminology Criteria for Adverse Event
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
IGA	Validated Investigator Global Assessment
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
Q1	25% Quartile
Q2W	Once Every 2 Weeks
Q3	75% Quartile
Q4W	Once Every 4 Weeks
RS	Randomization Set
SAE	Serious Adverse Event
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the detailed statistical analysis methods planned for the protocol entitled "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) sponsored by Suzhou Connect Biopharmaceuticals, Ltd.

This plan is prepared based on the Study Protocol Version 4.0 dated 01Aug2022 and the Case Report Form (CRF) Version 3.0 dated 27Apr2022. The planned analyses are mainly prepared for Stage 1. The analyses planned for Stage 2 will be described in subsequent update.

2. Study objectives

2.1. Primary Objective

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

2.2. Secondary Objectives

- To assess the safety and tolerability of CBP-201 in subjects with moderate to severe AD;
- To assess the pharmacokinetic (PK) profile of CBP-201 in subjects with moderate to severe AD;
- To assess the pharmacodynamic (PD) profile of CBP-201;
- To assess the immunogenicity of CBP-201.

3. Study design

3.1. Overall design

This study is a randomized, double-blind, multi-center, controlled study designed to assess the efficacy, safety, and PK profiles of CBP-201 in eligible subjects with moderate to severe AD. 255 subjects will be randomized in a 2:1 ratio to receive either CBP-201 300 mg Q2W or placebo.

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

Stage 1: This is a placebo-controlled part. Subjects who meet all the inclusion criteria and do not meet any of the exclusion criteria will be randomized in a 2:1 ratio into one of the following 2 groups to receive either investigational product or placebo treatment. The randomization will be stratified by the severity of their baseline disease (moderate [IGA=3] and severe [IGA=4]).

- Group A (CBP-201): the subjects will receive 600 mg of CBP-201 subcutaneously (4 ml in total, 2 injections of 2 ml each in different sites) on Day 1, followed by 300 mg of CBP-201 (2 ml) at Week 2 (W2) and every 2 weeks thereafter until W14;
- Group B (placebo): the subjects will receive 4 ml of placebo subcutaneously (2 injections of 2 ml

each in different sites) on Day 1, followed by 2 ml of placebo at W2 and every 2 weeks thereafter until W14.

Table 1: Dosing Regimen by Group 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. Treatment assignment for Stage 2 maintenance treatment will be performed based on whether a 50% or greater reduction in EASI score (i.e. EASI-50) is achieved.

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

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

Table 2: Dosing Regimen by Group 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.

All subjects (including the subjects who prematurely discontinue treatment) will be followed up for 8 weeks after the last dose.

The overall study design is shown in the diagram below:

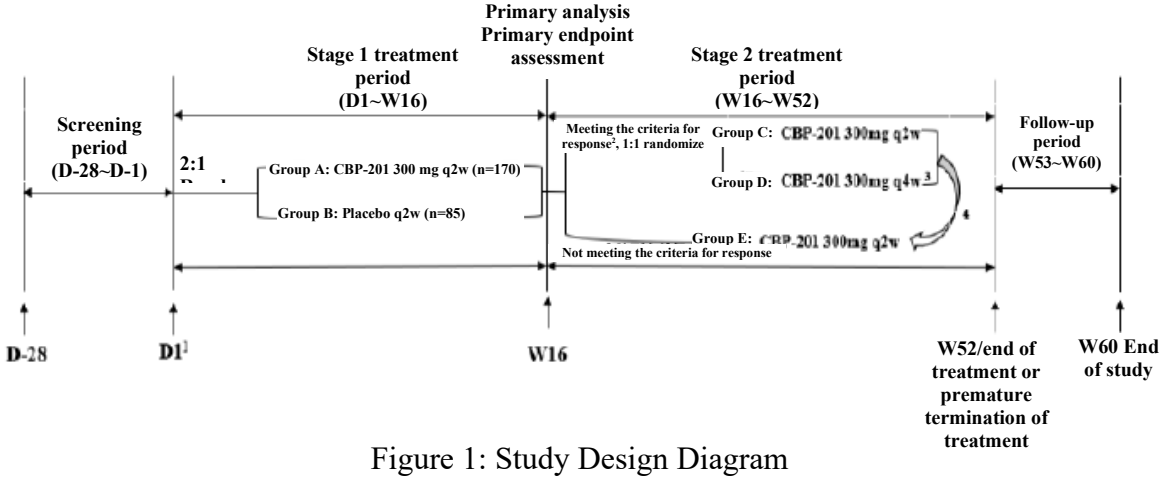

Figure 1: Study Design Diagram

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 greater reduction in the EASI score;

3： In order to maintain the study drugs administered every 2 weeks blind, at the middle of the 4-week dose interval, the subjects will receive 2 ml of placebo subcutaneously every 4 weeks until W50.

4： If subjects in group C and group D have not achieved EASI-50 in two continuous pre-administration efficacy assessments, they will be assigned to group E to be treated with 300 mg of CBP-201 subcutaneously every 2 weeks from the visit when EASI-50 is not achieved for the second time until W50.

3.2. Sample size

It is planned to enroll 255 subjects (in a 2:1 ratio, 170 subjects in the CBP-201 300 mg Q2W group, and 85 subjects in the placebo group) who will randomly receive either CBP-201 300 mg Q2W or placebo.

This sample size provides a power of approximately more than 90% to detect the difference between groups at a two-sided significance level of 5% under the assumption that 27% and 9% of subjects in the CBP-201 Q2W group and the placebo group can achieve an IGA score of 0-1 at W16 for the primary endpoint, respectively, accounting for a dropout rate of 15%.

Based on the results of another completed phase II international multicenter clinical study of CBP-201 in patients with moderate-to-severe atopic dermatitis, the proportion of subjects achieving the primary efficacy endpoint was 28.1% in the CBP-201 300 mg Q2W group and 10.7% in the placebo group, at a two-sided significance level of 0.05. 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 difference of 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.

4. Study Endpoints

4.1. Efficacy endpoints

4.1.1. Primary endpoint

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

4.1.2. Secondary endpoints

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;

4.1.3. 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 with recurrences 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 number of subjects with AD recurrence from baseline to W8;
- The number of subjects with AD recurrence from W8 to W16;

4.2. Safety endpoints

4.2.1. Drug Exposure and Compliance

Study drug exposure duration will be summarized by study stage. The duration will be calculated with the following formula:

Exposure duration = date of the last dose - date of the first dose + 14

For analysis of study drug exposure dose, total drug exposure dose of subjects will be summarized.

The compliance with the study drug and emollients (background treatment) will be calculated respectively. If the compliance is lower than 70% or higher than 130%, it will be determined as poor compliance.

Calculation formula of compliance with study drug: Compliance% = actual dose/planned dose * 100%.

Where the actual dose is the total dose of the drug actually used in Stage 1, and the planned dose is the total dose of the drug that should be used in Stage 1.

Calculation formula of compliance with emollients: Compliance% = number of days of using emollients as required by protocol/total number of days for which emollients should be used * 100%

4.2.2. Adverse events (AEs)

AEs

An adverse event refer to any untoward medical occurrence 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. See Section 10.1 of the protocol for details.

Treatment-emergent adverse event (TEAE)

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. The cut-off date of TEAEs in Stage 1 is immediately before the first dose for Stage 2 or 10 weeks (70 days) after end of dosing in Stage 1, whichever occurs first; for the subjects who discontinue administration in Stage 1, the cut-off date of TEAEs is the end of follow-up period.

Drug-related AEs

A drug-related AE refers to an AE whose relationship with the drug is related, possibly related or indeterminable.

The criteria for determination of the correlation of AEs with treatment are as follows:

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 preexisting 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 preexisting 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 preexisting 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 preexisting 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.

Serious Adverse Event (SAE)

An event will be considered an SAE if the following situations occur. See Section 10.1.2 of the protocol for definition of SAE. SAEs will be judged by investigators on CRF.

- 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 (i.e., 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.

Adverse Event of Special Interest (AESI)

AESIs in the study include: Conjunctivitis, keratitis, anaphylactic reaction, injection site reactions which persist over 24 h, AST/ALT increased > 5 × ULN, parasitic and opportunistic infection, pregnancy and symptomatic overdoses.

AEs leading to treatment discontinuation

In the study, action taken with study drug is drug discontinued or the subject will be withdrawn from treatment in response to these AEs.

4.2.3. Laboratory tests

Laboratory tests: Including hematology, blood biochemistry and urinalysis. The specific assessments are shown in Table as follows:

Table 3: 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	

4.2.4. Electrocardiogram (ECG)

12-lead ECG will be performed to collect ventricular rhythm, PR, QRS, QT, and QTcF.

4.2.5. Others

Vital signs

Vital signs include systolic and diastolic blood pressure, heart rate, body temperature, and respiratory rate.

Physical examination

Physical examination includes 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.

Other tests

ADA test.

4.3. PK/PD Endpoints

PK endpoints: To analyze the blood concentration of CBP-201, and calculate the PK profile at 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.

5. Statistical Hypothesis

The primary efficacy endpoint of the study is the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16. The following null and alternative hypotheses will be evaluated by statistical tests based on the efficacy endpoint. A two-sided significance level of 5% ($\alpha = 0.05$) will be adopted. If p value is ≤ 0.05, the null hypothesis will be rejected and it is considered that there is a statistically significant difference in IGA parameter between the CBP-201 300 mg Q2W group and the placebo group.

Null hypothesis (H0): Efficacy in the CBP-201 300 mg Q2W group = efficacy in the placebo group

Alternative hypothesis (H1): Efficacy in the CBP-201 300 mg Q2W group $\neq$ efficacy in the placebo group

6. Analysis datasets

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 datasets are included.

Screening set 1

It will include all subjects who have signed the informed consent form.

Randomization set 1 (RS1)

RS1 will include all subjects randomized at baseline (D1), regardless of whether they have received the study drug.

Full analysis set 1 (FAS 1)

FAS 1 will include all subjects who have been randomized and received at least one dose of the study drug. Subjects are analyzed within FAS 1 according to treatment assigned.

Per protocol set (PPS 1)

PPS 1 will include all subjects in FAS1 without any major protocol deviation that affects efficacy analysis. Major protocol deviations that affect efficacy analysis have been discussed and determined at the blinded data review meeting of the study on September 19, 2022. Minutes of the data review meeting will be presented in an annex.

By far, protocol deviations that affect efficacy analysis of the 255 subjects in Stage 1 are due to the following causes:

1. Missing dose (I. Missing W12 and W14 doses; II. Missing 3 doses in Stage 1, equivalent to a compliance with study drug lower than 70%);
2. Missing key efficacy results at W16 (both IGA and EASI missing);
3. Key efficacy results at W16 out of window (both IGA and EASI out of window >10 days);
4. Incorrect stratified randomization (only Stage 1);
5. Violation of inclusion and exclusion criteria (topical corticosteroids are used before baseline; baseline disease severity fails to meet the requirements);
6. Prohibited drugs (non-rescue treatment) that may affect efficacy

Safety set 1 (SS 1)

SS 1 will include all randomized subjects who have received at least one dose of study drug. Subjects are analyzed within SS 1 according to the treatment they actually received.

PK set 1 (PKS1)

PKS1 will include subjects who have received at least one dose of CBP-201 active drug and had at least 1 collected and analyzable PK sample.

Table 4: Analysis Population and Treatment Group in Stage 1

Analysis Populations	Treatment Groups	Analysis Stage
RS1/ FAS1/ PPS1/ SS1	1) Placebo	Stage 1 treatment period.

	2) CBP-201 300 mg Q2W	

7. Statistical methods

7.1. Overall statistical consideration

In the statistical tabulations, screening number of subjects is the universal unique identifier of subjects in the study.

General rules of descriptive statistics: Quantitative variables are described by mean, standard deviation, median, minimum, maximum, Q1 and Q3. In terms of rounding, the numbers of decimal places of the minimum and maximum are consistent with that of original value, while those of mean, medium, Q1, and Q3 are 1 more than that of the original value, and that of standard deviation is 2 more than that of the original value. Categorical variables are described by number and percentage of each category. The number of subjects is rounded to integer and percentage is rounded to one decimal place. It is unnecessary to present a percentage when the count is 0.

General rules of inferential statistics: Two-sided test is adopted for all statistical tests (unless otherwise specified). $P<0.05$ will be considered statistically significant (unless otherwise specified). P value is rounded to 4 decimal places. If $P < 0.0001$, it is presented as '< .0001'; if $P > 0.9999$, it is presented as '> .9999'.

The primary analysis of the study will be performed based on the data of Stage 1, that is, the placebo-controlled stage. The data analyzed will include all Stage 1 data from subjects who have completed Stage 1 or those who withdraw from Stage 1.

For 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.

Statistical analyses will be performed using SAS 9.4.

7.2. Methods for Data Processing

7.2.1. Convention of data processing and processing of missing data

The missing dates of AEs or concomitant medications/treatments will be imputed as follows. The imputation of missing dates will be used for classification only. When tabulations of relevant data are generated, unimputed dates will be still presented.

Missing of start date:

1) If the year and month are known and both are earlier than those of the first dose of the investigational product, the last day of the known month will be used for imputation.
2) If the year and month are known and same as those of the first dose of the investigational product, the start date is the date of the first dose of the investigational product (date refers to "month, day").

3) If the year and month are known and later than those of the first dose of the investigational product, it will be imputed with the first day of the known month.

4) If only the year is known and earlier than that of the first dose of the investigational product, "December 31" will be used for imputation.

5) If only the year is known and same as that of the first dose of the investigational product, the start date is the date of the first dose of the investigational product (date refers to "month, day").

6) If only the year is known and later than that of the first dose of the investigational product, it will be imputed with "January 1".

7) In other situations, the date of the first dose of the investigational product will be taken as corresponding start date.

Missing of end date:

1) If the year and month are known, it will be imputed with the last day of the known month.

2) If only the year is known, it will be imputed with "December 31".

3) If the end date imputed is earlier than the start date, the end date will be taken as corresponding start date.

4) Other conditions are regarded as missing.

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

7.2.2. Derived and Transformed Data

When the units of data from laboratories of different sites are inconsistent, the data will be converted according to international standard units.

Apart from the calculation of study endpoints based on the data collected from CRF, other data will not be derived or transformed.

Duration of exposure to drug (day) = date of the last dose - date of the first dose + 14.

7.3. Study Subjects

7.3.1. Subject disposition

Screening and randomization of subjects will be summarized based on Screening Set 1. The number and percentage of subjects will be calculated, and the reasons for screening failure will be presented; in addition, study drug discontinuation and study termination in both stages will be summarized based on RS1, and the number and percentage of subjects will be calculated. Subject disposition will be tabulated.

7.3.2. Protocol Deviations

All subjects who have protocol deviations in Stage 1 will be summarized based on RS1, the

number and percentage of subjects will be calculated and tabulated. In addition, all subjects with major protocol deviations that affect efficacy analysis will be summarized, the number and percentage of subjects will be calculated and tabulated.

7.3.3. Analysis datasets

The subjects who are included to SS1, FAS1, and PPS1 will be summarized based on RS1, and the number and percentage of subjects will be calculated.

7.3.4. Demographics and Baseline Characteristics

Analysis will be performed based on RS1.

Demographics such as age, gender, body height, body weight, and BMI will be summarized by descriptive statistics. The severity (moderate [IGA = 3] and severe [IGA = 4]) of atopic dermatitis (AD) at baseline will be summarized, and the number of percentage of subjects will be calculated. The baseline EASI/PP-NRS/BSA/SCORAD/POEM/DLQI will be summarized by descriptive statistics. Demographics and baseline characteristics will be tabulated.

7.3.5. Medical history of subjects

Analysis will be performed based on RS1.

Medical history will be coded based on Medical Dictionary for Regulatory Activities (MedDRA), and the number and percentage of subjects will be summarized by System Organ Class (SOC) and Preferred Term (PT). Medical history of allergic diseases and allergy history will be summarized separately, and the number and percentage of subjects will be calculated. Medical history will be ranked in descending order of total number of subjects by SOC and PT. All medical histories will be tabulated, and medical history of allergic diseases and allergy history will be tabulated separately.

7.3.6. Prior Medication, Concomitant Medication, and Prior and Concomitant Non-drug Therapies

Analysis will be performed based on RS1.

Prior and Concomitant Medications

Prior medication refers to a non-study drug that is started and ended before the first dose of study drug. Concomitant medication refers to a drug that is started at the time of or after the first dose of study drug, or a drug that is started before the first dose of the study drug and continued after the first dose of the study drug.

Prior and concomitant medications will be coded based on World Health Organization Drug Dictionary (WHODrug), and summarized based on ATC Level 2, ATC Level 4 (if the code is missing, it will be analyzed with the code of previous level) and PT. The number and percentage of subjects will be calculated. Prior and concomitant medications will be ranked in descending order of total number of subjects by ATC Level 2, ATC Level 4 and PT. In addition, they will be tabulated.

Prior and Concomitant Non-drug Therapies

Prior non-drug therapy refers to a therapy that is started and ended before the first dose of study drug. Concomitant non-drug therapy refer to a therapy that is started at the time of or after the first dose of study drug, or a therapy that is started before the first dose of the study drug and continued after the first dose of the study drug.

Prior and concomitant non-drug therapies will be coded by MedDRA. Concomitant non-drug therapies will be summarized by PT. The number and percentage of subjects will be calculated. Prior and concomitant non-drug therapies will be ranked in descending order of total number of subjects. They will be tabulated.

Rescue treatment

Rescue treatments during treatment period of Stage 1 will be summarized based on ATC Level 2, ATC Level 4 (if the code is missing, it will be analyzed with the code of previous level) and PT. The number and percentage of subjects will be calculated. These rescue treatments will be ranked in descending order of total number of subjects by ATC Level 2, ATC Level 4 and PT. They will be tabulated.

7.4. Efficacy analysis

Efficacy analysis in Stage 1 will be performed based on FAS1 and PPS1, mainly the FAS1.

In order to control the type I error rate for multiplicity, a fixed-sequence method will be used. First of all, the active treatment group and the placebo group will be compared for the primary efficacy endpoint; when the primary efficacy endpoint reaches statistical significance, the active treatment group and the placebo group will be compared for the key secondary efficacy endpoints according to the sequence specified in the protocol.

7.4.1. Visit window of efficacy analysis

For scheduled visits, the visit window for efficacy analysis will be based on the visit where the original data are collected. For unscheduled visits and premature withdrawal visit, the visit window for efficacy analysis will be based on the visit closest to the reference date (the previous visit when the distance is the same).

7.4.2. Intercurrent events and handling strategies

See table below for intercurrent events and handling strategies:

Label	Intercurrent event	Strategy	Remarks
Intercurrent event 1 (use of prohibited drugs/treatments specified in the protocol for which the study treatment must	• 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	Composite strategy	This type of intercurrent event occurs because of poor treatment effect, and should be treated as non-response.

Label	Intercurrent event	Strategy	Remarks
be early terminated due to poor treatment effect)	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.		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 for the treatment of AD (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 Event 1 due to poor treatment effect, with a major 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 for the treatment of AD (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 due to poor treatment effect before the W16 visit is more than 7 days, or the end date is less than 4 weeks away from 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 4 (early termination of treatment/EOT due to adverse	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	Composite strategy	This type of intercurrent event occurs because of poor safety of treatment, and should

Label	Intercurrent event	Strategy	Remarks
events)	treatment/EOT.		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 (W12 and W14) immediately before the W16 visit is missing or the administration in the Stage 1 treatment period is missing for ≥3 times.	Hypothetical strategy	The observed values are not used, and the J2R (jump to reference) method is used for imputation.
Intercurrent event 6 (use of prohibited drugs/treatments specified in the protocol not for poor treatment effect, with a major impact on the assessment of the primary endpoint)	The following prohibited drugs/treatments have been used before the W16 visit not because of the 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. Or The cumulative duration of use of the following prohibited drugs/treatments not due to the poor treatment effect before the W16 visit is more than 7 days, or the end date is less than 4 weeks away from the W16 visit: • Initiation of SIT, or dose up-regulation; • TCS or TCI (topical drugs can be used for AD lesion areas only); • Phototherapy (NBUVB, UVB, UVA1, PUVA), sunbed or any other LED therapies; • Bleaching baths more than 2 times a	Hypothetical strategy	The observed values are not used, and the J2R (jump to reference) method is used for imputation.

Label	Intercurrent event	Strategy	Remarks
	week; • Any drug for the treatment of AD (topical drugs can be used for AD lesion areas only) that may interfere with the evaluation of efficacy results or affect the evaluation of AD severity.		

7.4.3. Analysis of the primary efficacy endpoint and key secondary efficacy 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 primary endpoint	The difference in efficacy in patients aged 12 years and older with moderate to severe AD 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 RS1 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 7.4.2. 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.	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. **Sensitivity analysis 3:** For the subjects who are incorrectly stratified and randomized, the analysis will be performed using correct stratification factors and the same method as the main estimand; **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

Label of estimand	Description of estimand	Main estimator			Sensitivity/ Supplementary analysis
		Analysis sets	Rules for imputation	Model/method for the main analytical methods	
					reference) method will be used to impute the missing data in the test 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 average PP-NRS from baseline at W16; • The proportion of subjects	FAS (will include all subjects in RS1 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 7.4.2. 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.	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%	**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. **Sensitivity analysis 2:** For the subjects who are incorrectly stratified and randomized, the analysis will be performed using a correct stratification factor and the method the same as the main estimator; **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

Label of estimand	Description of estimand	Main estimator			Sensitivity/ Supplementary analysis
		Analysis sets	Rules for imputation	Model/method for the main analytical methods	
	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.			confidence intervals will be summarized.	missing data in the test group.

In the J2R (jump to reference) method, when the data of subjects of the active treatment group are missing, it is assumed that their statistical results are the same as those of the placebo group, that is, it is considered that the pharmacological action of the drug for the active treatment group is the same as that of the placebo group. PROC MI will be used for J2R imputation, and the missing data of the active treatment group will be imputed with the results obtained by posterior predictive distribution of the placebo group. Markov Chain Monte Carlo (MCMC) will be used to extend the data, and a regression method will be used to generate M datasets (M is set as 30 in this study). The imputed variables should include: treatment group, stratification factor (severity of baseline disease), baseline value of corresponding endpoint and measurement at each visit. Random seed is the earliest date of the first dose to all subjects.

Table 5 Random Seeds of Multiple Imputation

Endpoints	Random Seeds
IGA	Minimum date of the first dose
EASI	Minimum date of the first dose + 1
PP-NRS	Minimum date of the first dose + 2
BSA	Minimum date of the first dose + 3
SCORAD	Minimum date of the first dose + 4
DLQI	Minimum date of the first dose + 5
POEM	Minimum date of the first dose + 6

Tipping point analysis: To evaluate the robustness of the primary efficacy endpoint analysis, tipping point analysis should be performed on the primary efficacy endpoint at W16. The tipping point method is binary, that is, the assumptions of missing values of the active treatment group and the placebo group are mutually independent. Assuming that the response rate of missing values of the two groups increases by 10% from 0 to 100%, the subjects with a missing response in the two groups at a certain percentage will be randomly assigned as responders and non-responders in 30 imputed datasets randomly generated by the binomial distribution. Then the same analysis method as that for the primary study endpoint will be used to obtain the comparison results between the two groups in each imputed dataset. Finally, Rubin's Rule will be used to pool these results. If there is a pair of assumed response rate that overturns the study conclusion, that is, p value is more than 0.05, the two assumed response rates will be the cut-off points.

Subgroup analysis will be performed on the primary efficacy endpoint (the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16) and the key secondary efficacy endpoint (the proportion of subjects achieving EASI-75 at W16) by gender (male/female), severity of baseline disease (moderate [IGA = 3]/severe [IGA = 4]), history of allergic diseases or allergy history (yes/no), baseline EASI (< baseline median EASI/≥ baseline median EASI), baseline PP-NRS (< baseline median PP-NRS/≥ baseline median PP-NRS). The analytical method is the same as the primary analysis method for the primary efficacy endpoint and the key secondary efficacy endpoint. The subjects with missing

subgroup variables will not be included to analysis.

Sensitivity analysis will be performed on the primary efficacy endpoint (the proportion of subjects whose IGA score is 0-1 and decreased by ≥ 2 points from baseline at W16) and the key secondary efficacy endpoint (the proportion of subjects achieving EASI-75 at W16) using the correct stratification factor and the method the same as the main estimator.

7.4.4. Other efficacy endpoint analysis

The categorical efficacy endpoint analysis will be performed using the same method as the primary efficacy endpoint analysis.

The continuous efficacy endpoint analysis will be performed using the same method as the secondary efficacy endpoint analysis.

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.

The number of AD recurrence, the number of subjects with AD recurrence, and the number of days of AD recurrence in Stage 1, from baseline to W8, from W8 to W16 will be analyzed. The total number of AD recurrence in each stage will be summarized. AD recurrence will be summarized by the number of recurrences, that is, 0, 1, 2 and ≥ 3. The number and percentage of subjects will be calculated. Chi-squared test will be adopted to compare whether the differences between the two groups are statistically significant. The total number of subjects with AD recurrence in each stage will be summarized, and the number and percentage of subjects will be calculated. Chi-squared test will be performed to compare whether the differences between the two groups are statistically significant. The number of days of AD recurrence in each stage will be summarized by descriptive statistics.

7.5. Safety Analysis

7.5.1. Drug exposure and compliance

Study drug exposure will be analyzed based on SS1. Study drug exposure duration and exposure dose during treatment period of Stage 1 will be summarized by descriptive statistics.

The compliance with the study drug and emollients (background treatment) in Stage 1 will be summarized by descriptive statistics. The subjects with a compliance < 70%, ≥ 70% and ≤ 130%, and > 130% will be summarized, and the number and percentage of subjects will be calculated. Subjects’ compliance with the study drug and emollients (background treatment) will be tabulated.

7.5.2. AEs

AEs will be analyzed based on the SS1

AEs will be coded using MedDRA.

The occurrence of overall AEs will be summarized to generate summary tabulations of TEAEs. TEAEs of special interest and drug-related AESIs will be summarized. The numbers of subjects with various AEs, numbers and incidences of events will be calculated.

AEs, drug-related AEs, SAEs, AESIs, AEs leading to death, AEs leading to treatment discontinuation, injection site AEs, CTCAE grade 3-5 AEs, AEs with an incidence of > 5%, and AD recurrence-related AEs will be tabulated.

The incidences of the following TEAEs will be summarized by SOC and PT, the numbers of subjects with various AEs, and the numbers and incidences of events will be calculated. They will be ranked in descending order of total number of subjects by SOC and PT.

1) TEAEs;
2) Drug-related AEs;
3) SAEs;
4) Drug-related SAEs;
5) AEs leading to death;
6) AEs leading to treatment discontinuation;
7) AEs leading to treatment interruption;
8) AESIs;
9) Drug-related AESIs;
10) Injection site AEs;
11) CTCAE grade 3-5 AEs;
12) AEs with an incidence of > 5%;

In addition, the incidences of TEAEs, AESIs, and injection site AEs will be summarized by CTCAE Grade, correlation with study drug, SOC and PT, and the number and percentage of subjects will be calculated.

A subject with an AE of the same SOC and PT more than once will have that event counted only once within each SOC and PT.

7.5.3. Laboratory test results

Laboratory test results will be analyzed based on the SS1.

The hematology, blood biochemistry and urinalysis parameters at baseline and each visit and their changes from baseline at each visit will be summarized by descriptive statistics.

The number and percentage of subjects whose hematology, blood biochemistry and urinalysis parameters at baseline and each visit are below, within and above the normal range will be summarized.

Pre-treatment and post-treatment laboratory test results are classified into abnormal with clinical significance, abnormal without clinical significance, normal, and not tested in an order of abnormal with clinical significance > abnormal without clinical significance > normal > not tested. Then shift tables are generated. The shift tables are generated based on CTCAE 5.0.

All laboratory test results and abnormal laboratory test results for hematology, blood biochemistry, urinalysis and urine pregnancy will be tabulated.

Qualitative laboratory test results will be summarized by visit. The number and percentage of subjects for each category will be calculated and tabulated.

7.5.4. ECG

ECG findings will be analyzed based on the SS1.

Ventricular rhythm, PR, QRS, QT and QTcF results at each post-baseline visit and their changes from baseline at each visit will be summarized by descriptive statistics. The analysis of variance will be used to detect possible difference between groups.

Special attention will be paid to QTcF interval prolongation:

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms
- Increase in QTcF interval from baseline > 30 ms
- Increase in QTcF interval from baseline > 60 ms

Pre-treatment and post-treatment ECG results are classified into abnormal with clinical significance, abnormal without clinical significance, normal, and not tested in an order of abnormal with clinical significance > abnormal without clinical significance > normal > not tested. Then shift tables are generated.

ECG results of QTcF interval prolongation will be tabulated. All ECG results and clinically significant abnormal ECG results will be tabulated.

7.5.5. Other safety evaluation

The following analyses are based on SS1.

Physical examination

Physical examination results at each visit in Stage 1 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All physical examination results and abnormal physical examination results with clinical significance will be tabulated.

Vital signs

The vital signs at baseline and their changes from baseline at each visit of Stage 1 will be summarized by descriptive statistics. The analysis of variance will be used to detect possible difference between groups.

Vital sign results at each visit of Stage 1 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All vital sign results and abnormal vital sign results with clinical significance will be tabulated.

Eye examination

Eye examination results at each visit of Stage 1 will be classified into abnormal with clinical significance, abnormal without clinical significance, normal and not tested. The frequency and percentage of each category will be summarized.

All eye examination results and abnormal eye examination results with clinical significance will be tabulated.

ADA test

See PK/PD statistical analysis plan for details.

7.6. Pharmacokinetics (PK) analysis

See PK/PD statistical analysis plan for details.

7.7. Pharmacodynamics (PD) and Biomarker Analysis

See PK/PD statistical analysis plan for details.

7.8. Changes to Planned Analysis in the Protocol

Description of intercurrent event 6 and strategies for managing intercurrent event 6 is added.

8. References

Guidelines for Management and Statistical Analysis Plan of Drug Clinical Trial Data 2021.