Statistical Analysis Plan

Suzhou Connect Biopharmaceuticals, Ltd
Protocol Number: CBP-201-WW001

A Randomized, Double-Blind, Placebo-Controlled Multi-Centered Study of the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of CBP-201 in Adult Subjects with Moderate to Severe Atopic Dermatitis

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan v3 (dated Oct 15, 2021) for protocol CBP-201-WW001

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List of Abbreviations and Definitions of Terms

Abbreviation	Term
AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
AESI	AE of special interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NRI	Non-responder Imputation
OC	Observed cases
ODS	Output Delivery System
PD	Pharmacodynamic
POEM	Patient-Oriented Eczema Measure
PK	Pharmacokinetic
PP-NRS	Peak Pruritus Numerical Rating Scale
PPS	Per-Protocol Set
PT	Preferred Term
RTF	Rich-text-formatted
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCORAD	Severity scoring of AD
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TCS	Topical corticosteroids

TEAE	Treatment-emergent AE
vIGA-AD™	Validated Investigator Global Assessment scale for Atopic Dermatitis
VS	Vital Signs
WOCF	Worst Observation Carried Forward
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) describes the statistical rationale, methods, rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol CBP-201-WW001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This SAP is based on study Protocol Amendment 3.0, dated May 28, 2020.

This SAP provides additional details concerning the statistical analyses outlined in the protocol and reflects any changes to the protocol from any amendments. This plan will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein.

The analyses for the pharmacokinetic (PK) and pharmacodynamic (PD) data will be described in a separate analysis plan. The current plan will cover details concerning data displays and descriptive summaries of the PK and PD data.

2. Protocol Objectives

A. Primary Objective

Assess the efficacy of various treatment regimens of CBP-201 in subjects with moderate to severe atopic dermatitis (AD).

B. Secondary Objectives

In subjects with moderate to severe AD,

- Assess the safety and tolerability of various treatment regimens for CBP-201.
- Characterize the steady-state PK profile of various treatment regimens for CBP-201.

C. Exploratory objectives

In subjects with moderate to severe AD,

- Characterize the PD profile of various treatment regimens for CBP-201.
- Characterize the PD/efficacy relationship of various treatment regimens for CBP-201.

Relevant analyses for PK/PD related objectives will be covered in a separate plan.

3. Study Endpoints

A. Primary Efficacy Endpoint

EASI-overall: percentage reduction in Eczema Area and Severity Index (EASI) from Baseline to Week 16.

B. Secondary Efficacy Endpoints

- IGA (0-1): proportion of subjects with both Investigator Global Assessment (IGA) score 0 to 1 (clear; almost clear) and a reduction of ≥ 2 points at Week 16.
- EASI:
  - EASI-50: proportion of subjects achieving ≥ 50% reduction of EASI score from baseline at Week 16.
  - EASI-75: proportion of subjects achieving ≥ 75% reduction of EASI score from baseline at Week 16.
  - EASI-90: proportion of subjects achieving ≥ 90% reduction of EASI score from baseline at Week 16.
- Change from Baseline to Week 16 in weekly average Peak Pruritus Numerical Rating Scale (PP-NRS).

C. Other Efficacy Endpoints

- EASI-50/EASI-75/EASI-90 at Week 20
- EASI-100 at Week 16 and Week 20
- IGA 0: proportion of subjects with IGA score 0 at Week 16 and Week 20.
- Proportion of subjects achieving ≥ 2-point improvement in IGA from Baseline to Week 16 and Week 20.
- Change from Baseline to Week 20 in weekly average PP-NRS.
- Proportion of subjects achieving ≥ 3-point reduction in weekly average of PP-NRS from Baseline to Week 16 and Week 20.
- Proportion of subjects achieving ≥ 4-point reduction in weekly average of PP-NRS from Baseline to Week 16 and Week 20.
- Change in Patient Oriented Eczema Measure (POEM) from Baseline to Week 16 and Week 20.
- Change in percentage body surface area (BSA) of AD involvement from Baseline to Week 16 and Week 20.
- Change in Severity scoring of AD (SCORAD) from Baseline to Week 16 and Week 20.
- Change in Dermatology Life Quality Index (DLQI) from Baseline to Week 16 and Week 20.
- Number of subjects with AD flares from Baseline to Week 8 and from Week 8 to Week 16 and Week 20.
- Number of AD flares (defined as escalation of therapy evidenced by Topical corticosteroids (TCS) usage) from baseline through Week 16.
- Number of days with AD flare through Week 16.

D. Safety Endpoints

- Adverse events (AEs) reported
- Vital Signs (VS)
- Physical examinations

- Injection site changes
- Safety laboratory parameters
- Electrocardiogram (ECG) parameters
- Number (%) of subjects displaying positive anti-drug antibodies (ADA)

4. Study Design

A. Design Overview

This is a phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, PD and PK profile of CBP-201 administered to eligible adult subjects with moderate to severe AD. The study period includes a treatment period of 16 weeks and a follow-up period of 8 weeks.

Approximately 220 subjects who meet eligibility criteria and consent to participate in the study are randomly assigned in a 1:1:1:1 ratio to one of the following treatment groups:

- CBP-201 1800 mg (150 mg Q2W): CBP-201 600 mg (4 vials) on D1, 1 vial of CBP-201 and 1 vial of placebo on W2 and the same dose Q2W thereafter through W16. Total CBP-201 dose over 16 weeks: 1800 mg.
- CBP-201 3000 mg (300 mg Q2W): CBP-201 600 mg (4 vials) on D1, CBP-201 300 mg (2 vials) on W2 and Q2W thereafter through W16. Total CBP-201 dose over 16 weeks: 3000 mg.
- CBP-201 1800 mg (300 mg Q4W): CBP-201 600 mg (4 vials) on D1, placebo (2 vials) on W2, CBP-201 300 mg (2 vials) on W4, W8, W12 and W16, alternating with placebo (2 vials) on W6, 10, and 14. Total CBP-201 dose over 16 weeks: 1800 mg.
- Placebo: 4 vials on D1, 2 vials on W2 and Q2W thereafter through W16.

B. Study Population

Study subjects are adults between 18 and 75 years old (both included) at the screening visit (Screening) with AD (according to American Academy of Dermatology Consensus Criteria, Eichenfield 2014) present for at least 1 year prior to the baseline visit (Baseline). In terms of AD, subjects must have an inadequate response to AD treatment with a topical regimen of corticosteroids, phosphodiesterase inhibitors or calcineurin inhibitors, or for whom topical treatments are otherwise medically inadvisable, and have IGA score ≥ 3, EASI score ≥ 16, and BSA for total AD involvement $\geq 10\%$ at Screening and Baseline.

C. Sample Size Determination

A sample size of 220 (55 per arm, providing approximately 44 completers per treatment group assuming 20% dropout rate) will provide 95% power to detect at treatment effect on the primary endpoint of percentage reduction of EASI at week 16 between the CBP-201 300 mg Q2W vs. Placebo. This power calculation

is based on the use of a two-sided two-sample t test at the alpha=0.05 level of significance. Based on the preliminary results at Week 4 and empirical data, the mean between-group difference is assumed to be equal to 35 percentage points and the pooled standard deviation is assumed to be 45% using 2-sample independent t-test.

D. Treatment Randomization

Patients will be randomized at a 1:1:1:1 ratio into the following 4 groups: CBP-201 1800 mg (600mg load D1 then 150 mg Q2W), CBP-201 3000 mg dose (600mg load D1 then 300 mg Q2W), CBP-201 1800 mg dose (600mg load D1 then 300 mg Q4W), or placebo, respectively. The randomization is not stratified.

E. Assessment Schedule

The date at which the subject is randomized will be referred to as the "Baseline/Day 1" visit. Subjects will be requested to attend the scheduled visits for the Treatment Period every 2 weeks from their Baseline/Day 1 visit through Week 16. The acceptable visit window for scheduled visits during the Treatment Period is ± 2 days. After Week 16 of treatment, subjects will no longer receive any treatments but will return for an additional 8 weeks for follow-up visits. The acceptable visit window for scheduled visits during the Follow-up Period is ± 3 days.

In the case of an early termination (ET) from the study for any reason, study completion assessments should be performed as detailed for the study completion visit and should be completed within 7 days of the ET, whenever possible.

F. Clinical Trial Material

CBP-201 is provided as a single-use 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution. Placebo is provided as a single-use 2 mL vial containing 1.2 mL solution without CBP-201 and is identical in appearance. The protocol provides additional product details in Section 9.

5. General Analytical Considerations

A. Data Sources and General Rules

Data are recorded on electronic case report form (eCRF) for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable. Laboratory data, ECG and blood samples data are collected separately by the selected vendors. Section 12 of the protocol provides additional details regarding data handling and record keeping.

Statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analysis will be performed using SAS Version 9.4 or higher with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and SAS programmers.

All continuous study assessments will be summarized by treatment and time point (as applicable) using the descriptive statistics n, mean, standard deviation (SD), median, and range (minimum, and maximum). Categorical assessments will be summarized by treatment and time point (as applicable) using frequency counts and rates of occurrence (%). The formal statistical comparison will be performed on the primary efficacy endpoints only, while descriptive statistics, together with Clopper-Pearson exact confidence interval (CI) for proportions, will be provided. All statistical tests will be conducted using 2-sided tests with 5% Type 1 error rates unless otherwise stated.

B. Definition of Baseline and Study Day

Baseline is defined as the last non-missing assessment prior to the date of the first administration of study treatment. In particular, the PP-NRS assessment will be collected once daily based on peak pruritus over the last 24 hours. The baseline PP-NRS will be defined as the mean value of all entries (at least 4 entries) during last week preceding randomization from Day -7 to Day -1. If a subject missed more than 3 entries during the 7 days before Baseline visit, the baseline PP-NRS value will be considered as undefined (missing) for the subject.

Reduction from baseline will be defined as: Baseline value – post-Baseline value. The percent reduction from Baseline will be calculated as reduction from Baseline divided by the Baseline value, expressed as a percentage.

Change from Baseline is defined as: post-Baseline value – Baseline value. The percent change from Baseline will be calculated as change from Baseline divided by the Baseline value, expressed as a percentage.

Day 1 is defined as the date of first administration of study treatment. Study day is calculated relative to the date of Day 1.

C. Analysis Visit Window

Because all study medication will be administered at the study center via subcutaneous (SC) injection every 2 weeks, all efficacy and safety endpoints will be summarized and analyzed according to their nominal visit as assigned, except for ET visits. ET visits will be re-mapped to the last nominal visit number + 1. For example, if a subject attended Week 2, Week 4, Week 6 and then early terminated, the early termination visit will be re-mapped and analyzed as Week 8. No analysis visit window mapping based on actual study day will be performed other than that for ET visits.

Unscheduled visits will not be re-mapped and will not be included in table summaries. They will only be listed.

D. Multiple Study Centers

This study will be conducted by multiple investigators at multiple centers internationally. Descriptive summaries of the primary and secondary efficacy endpoints will be presented for each individual study center to evaluate potential heterogeneity across sites. Baseline characteristics and key safety endpoint may be presented for each study center as appropriate. The implications of any significant heterogeneity on the assessment of overall efficacy will be explored.

E. Covariate Adjustment in Primary Analysis

The primary efficacy analyses will adjust for baseline EASI score and baseline IGA score (moderate, severe) as described in Section 8 Efficacy Analyses below.

F. Subgroup Analysis

Exploratory subgroup analysis of the primary or other efficacy endpoints based on demographic factors or other covariates may be performed on an ad hoc basis, using descriptive statistics. Grouping factors may include:

- Age
- Sex
- Race
- Ethnicity
- Baseline IGA Score

In addition, exploratory subgroup analysis of EASI-100 (proportion of subjects achieving 100% reduction of EASI score from baseline), proportion of $\geq$ 3-point and $\geq$ 4-point reduction in weekly average of PP-NRS at Week 16 will performed using similar method as described for binary secondary efficacy endpoints (IGA response, EASI-50, 75, 90 response), among subjects enrolled in China. Other exploratory subgroup analysis of efficacy or safety endpoints may also be performed among subjects enrolled in China on an ad hoc basis. No formal statistical comparison will be performed.

G. Interim Analyses

No formal interim analysis of efficacy is planned.

H. Multiple Comparisons and Multiplicity

The primary efficacy endpoint will be analyzed using the analysis of covariance (ANCOVA) statistical method. Pairwise comparisons for each CBP-201 group vs. placebo will be performed and a serial gatekeeping procedure will be used for multiplicity adjustment. From the highest dose (300 mg Q2W) to the lowest dose frequency (300 mg dose Q4W), each CBP-201 group will be compared with the placebo group in order, until statistical significance at 0.05 level is not achieved. This procedure helps preserve the alpha at 0.05 level.

I. Analysis Populations

The following analysis populations will be defined for the study:

Table 1. Analysis Populations

Analysis Populations	Description
Screened	All Subjects Screened (Screened) set will contain all subjects who signed informed consent.
Randomized	All Randomized Set (Randomized) will contain all subjects who are randomized into the study, no matter whether they were treated or not.
Safety Set (SS)	The SS will include all randomized subjects who received at least part of an SC dose of study treatment.
PK Set (PKS)	The PKS will include all randomized subjects who received at least 1 dose of active study treatment and have at least 1 PK sample collected and analyzable.
Full Analysis Set (FAS)	The FAS will include all randomized subjects who received at least part of an SC dose of study treatment.
Per Protocol Set (PPS)	The PPS will contain a subset of FAS subjects who do not have any major protocol deviations that could influence the validity of the data for the primary endpoint. A subject may be excluded from the PPS if any of the following criteria (but not limited to) are met:

	• Failure to meet Inclusion/Exclusion criteria • Usage of restricted medications/treatments • Failure to have an assessment for EASI at Week 16 • Insufficient exposure to trial treatment The composition of PPS will be determined and documented in blind reviews of the database conducted prior to database lock and unblinding. Subjects who used permitted rescue medications will be included in PPS, with assessments after the initiation of rescue medications set to missing. Handling of missing data after the initiation of rescue medications is described in Section J below.

All safety assessments and baseline characteristics will be summarized using the SS. PK analyses will be performed using the PKS. PK and safety analysis will be based on the actual treatment received. PD and efficacy analyses will be performed using the FAS, based on planned treatment assignment (i.e., "as randomized"). Primary efficacy analysis will also be conducted in PPS as supportive, based on planned treatment assignment.

Each active dose cohort will be presented separately, along with a combined active dose group.

Membership in the analysis populations will be determined before unblinding.

J. Missing Data

Missing efficacy outcomes will be handled as following:

- For analysis of binary efficacy endpoints (IGA response, EASI-50, EASI-75, EASI-90, EASI-100, IGA score 0, IGA ≥2 reduction, PP-NRS ≥3 reduction, PP-NRS ≥4 reduction), subjects who have no data at a specific scheduled visit will be imputed using non-responder imputation (NRI).
    - NRI (Non-responder imputation): Subjects with missing value at the specific timepoint will be considered as non-responders. Assessments for subjects who used rescue medications (either permitted or prohibited) will be treated as missing and imputed using NRI for all time points after the initiation of rescue medications.
- For all numerical summary of the primary efficacy endpoint (change in EASI) and the secondary efficacy endpoint analysis items (PP-NRS, POEM, affected BSA, SCORAD, DLQI), the missing individual values at all time points will be imputed using the post-baseline last observation carried forward (LOCF) approach. WOCF and multiple imputation (MI)

will also be used as sensitivity analysis for primary efficacy endpoint at Week 16.

- LOCF (Last observation carried forward): The last observed post-baseline value will be carried forward for any subsequent missing values through Week 16, with assessments after the first use of rescue medication (either permitted or prohibited) set to missing. Subjects with no post-baseline assessments will be considered as missing for the relevant analyses.

- WOCF (Worst observation carried forward): The worst observed post-baseline value will be assumed for any missing value at Week 16, with assessments after the first use of rescue medication (either permitted or prohibited) set to missing. Subjects with no post-baseline assessments will be considered as missing for the relevant analyses.

- MI: Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods.

  MI procedures for *EASI score at Week 16*:
  Missing values for EASI scores through week 16 (with assessments after the first use of rescue medication [either permitted or prohibited] set to missing) will be imputed separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method. Intermittent missing EASI scores through week 16 will be imputed separately for each treatment group. 50 copies of the dataset with monotonic missing pattern will be generated. For each of the 50 datasets, missing values at scheduled visits (Weeks 2, 4, 8, 12, and 16) will be imputed using a monotone regression model including treatment, baseline IGA score (moderate, severe), baseline EASI score, and EASI scores at the previous scheduled visits. Absolute reduction and percent reduction from baseline in EASI score will be derived based on the imputed datasets.

  Example SAS code is as follows:

```
PROC MI DATA = MI1 OUT = MI2 SEED = 975311 NIMPUTE = 50
MINIMUM =0 MAXIMUM = 72 ROUND = 1 NOPRINT;
      BY TRTP;
      MCMC IMPUTE = MONOTONE;
      VAR BASEIGA BASEEASI W2 W4 W8 W12 W16;
RUN;
```

```
PROC MI DATA = MI2 OUT= MI3 SEED = 975311 NIMPUTE = 1
MINIMUM =0 MAXIMUM = 72 ROUND = 1 NOPRINT;
      BY _IMPUTATION_;
      CLASS TRTP BASEIGA;
      MONOTONE REGRESSION;
      VAR TRTP BASEIGA BASEEASI W2 W4 W8 W12 W16;
RUN;
```

A pre-specified seed number of 975311 will be used in all imputation procedures as described above. Alternative model specifications may be used based on the actual data if there is an issue in model convergence.

All other efficacy endpins not mentioned above will be analyzed as OC with no imputation. No imputation of safety endpoints will be used unless otherwise specified.

K. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. In general, they will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject (e.g., further ordering by lab test names in the lab listings).

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections.

6. Subject Characteristics

A. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each treatment group and for the overall population using the SS by descriptive statistics.

- Age (years)
- Sex
- Race
- Ethnicity
- Country
- Weight (kg)
- Height (cm)

- Body mass index (BMI) (kg/m^2)
- Baseline IGA Score
- Baseline Total EASI Score
- Baseline BSA Involvement (%)

B. Medical / Surgical History and Concurrent Procedures

Medical / surgical history (including history of AD) and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher, graded using CTCAE grade, and presented in a by-subject listing.

C. Prior and Concomitant Medication

Prior (within the previous 30 days and with stop dates prior to first administration of study treatment) and concomitant (ongoing or with stop dates on or after first administration of study treatment) medications will be presented in a by-subject listing for each treatment group, medications used as rescue treatment will be flagged. Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) version March 2020 terminology.

For the determination of prior vs. concomitant medications, the following rules regarding the stop date will be applied:

- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.

Additionally, concomitant medications and medication used as rescue treatment will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using WHO-DD Anatomical Therapeutic Chemical (ATC) classes and preferred terms (PT).

7. Subject Accountability

A. Disposition

The numbers of subjects screened, who screen fail (along with the reason), who were randomized, completed the study, and discontinued, along with reasons for discontinuation, will be tabulated using frequencies and percentages, overall and by treatment group, as well as pooled CBP-201 group. The number of subjects in

each analysis population and who were excluded from PPS (overall and by reason for exclusion), will be summarized as well.

Due to the outbreak of COVID-19 pandemic, COVID-19 related subject disposition events will be further summarized per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (thereinafter referred to as FDA COVID-19 Guidance)[1], for the following:

- Number of subjects discontinued from treatment or study for reasons related to COVID-19
- At each scheduled visit:
  - Number of subjects with visits missed due to COVID-19
  - Number of subjects with any efficacy assessments not done due to COVID-19

B. Protocol Deviations and Population Inclusions

All protocol deviations will be classified and documented before database lock and will be discussed in the CSR. All protocol deviations, both minor and major, will be presented in a data listing.
Protocol deviations attributable to the COVID-19 pandemic regardless whether deemed major or minor will be provided in a separate listing if deemed necessary.

8. Efficacy Analyses

A. Efficacy Outcomes

- **EASI** is a validated scoring system that grades the severity and extent of AD and erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head/neck, trunk, upper and lower extremities. It is a composite index with scores ranging from 0 to 72; higher scores reflecting the worse severity of AD.
- **IGA** Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) is a 5-point scale to measure disease severity: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe.
- **SCORAD** is clinical tool for assessing the severity (extent/intensity) of AD and subjective signs/symptoms (e.g. pruritus/insomnia). The extent of lesions is scored by applying the rule of nines. The intensity is determined by grading each of the 6 items on a scale from 0 to 3 (erythema, edema, oozing/crusting, excoriations, lichenification and dryness). There are 3 components to the assessment: A = sum of extent, B = intensity, and C = subjective symptoms. The

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency, updated 21 September 2020

SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103; higher scores reflecting the worse severity of AD.

- **Percent BSA of AD involvement** will be assessed for each section of the body (head and neck, anterior trunk, back, upper limbs, lower limbs, genitals) and combined.
- **PP-NRS** is a single self-reported item designed to measure peak pruritus or 'worst' itch, over the previous 24 h on a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable". For PP-NRS from subject daily diary, the weekly average PP-NRS will be analyzed as efficacy endpoint, and calculated as following:
  - For Treatment Period: Baseline (Day -7 to -1), Week 1 (Day 1 to 7), Week 2 (Day 8 to 14), Week 3 (Day 15 to 21), Week 4 (Day 22 to 28), etc., until Week 16 (Day 106 + for subjects not enrolled into Follow-up Period, Day 106 to Day of Week 16 visit for subjects enrolled into Follow-up Period).
  - For Follow-up Period: Week 17 (Day of Week 16 visit +1 to Day 119), Week 18 (Day 120 to 126), etc., until Week 24 (Day 162 to End of Study Visit).
  - Subjects must complete at least 4 NRS entries to calculate the weekly average. The weekly average will be considered missing if more than 3 entries are missing for that weekly interval.
- **POEM** is a 7-item questionnaire assessing disease symptoms on a 0 to 4 scale (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease); higher scores indicative of poorer quality of life.
- **DLQI** is 10-item questionnaire assessing the impact of AD on quality of life (QOL) over the past week, with an overall scoring of 0 (absent disease) to 30 (severe disease); higher scores indicative of poorer QOL.

The scoring of each question is as follows:

Response	**Score**
Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

The scoring of DLQI will follow the developer's manual2. Specifically:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
- If two or more questions are left unanswered the questionnaire is not scored.
- If question 7 is answered 'yes' this is scored 3. If question 7 is answered 'no' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If "Not relevant" is ticked, the score for Question 7 is 0. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
- If two or more response options are ticked, the response option with the highest score should be recorded.
- If there is a response between two tick boxes, the lower of the two score options should be recorded.

B. Primary Efficacy Outcome Analysis

The primary efficacy endpoint will be comparing percentage reduction in EASI from baseline to Week 16 for each CBP-201 regimen versus placebo.

The primary efficacy analysis will consist of three hypotheses, which will be fully adjusted for multiplicity using a serial gatekeeping procedure at the 5% level of significance as long as the previous hypothesis is rejected. The order of testing will be based on the difference between the CBP-201 vs. placebo at Week 16 for the following regimens in descending order:

1. After a 600 mg loading dose, 300 mg dose Q2W
2. After a 600 mg loading dose, 150 mg dose Q2W
3. After a 600 mg loading dose, 300 mg dose Q4W

The data will be analyzed using the analysis of covariance (SAS PROC MIXED PROCEDURE for ANCOVA) model, with treatment, baseline IGA (moderate, severe) and baseline EASI; a 95% CI for the difference in % reduction in EASI from baseline to Week 16 between each CBP-201 regimen vs. placebo will be provided. Subjects with missing EASI score at Week 16 will be imputed using LOCF in the analysis.

The model will be fitted using the SAS syntax below:

```
PROC MIXED DATA= TEST;
        CLASS TRTP BASEIGA;
```

[2] DLQI Instructions for use and scoring. A Y Finlay, G K Khan April 1992. Available at: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index

```
        MODEL PCHG = TRTP BASEIGA BASEEASI;
        LSMEANS TRTP / DIFF CL PDIFF;
RUN;
```

The primary efficacy analysis will be based on FAS (LOCF) and the statistical conclusion will be based on FAS only. The testing will also be performed on PPS (OC) for supporting purpose and no multiplicity justification will be further conducted on analyses using PPS.

Sensitivity analyses using WOCF and MI will also be performed on FAS. In addition, analysis based on OC including actual values after the first use of rescue medication (either permitted or prohibited), will also be performed on FAS as sensitivity analysis.

Observed value, change from Baseline and percent change from Baseline in EASI scores will also be summarized using descriptive statistics by visit in FAS (OC, and LOCF) and PPS (OC).

C. Secondary Efficacy Outcome Analyses

For binary secondary efficacy endpoints (IGA response, EASI-50, 75, 90 response), counts, percentage, and 95% CIs obtained based on the Clopper-Pearson method (SAS PROC FREQ PROCEDURE, exact binomial) will be presented for each CBP-201 regimen and placebo, respectively, based on FAS; p-value for pairwise comparisons for each CBP-201 group vs. placebo will also be presented in an exploratory manner. For responder endpoints, missing value will be imputed using NRI.

For change from baseline to Week 16 in weekly average PP-NRS, the method for statistical analysis is similar as described above for primary efficacy endpoint, with replacement of PP-NRS by EASI in the model, using LOCF for all visits based on FAS and also WOCF at Week 16 as sensitivity analysis..

Proportion of subjects achieving IGA (0-1), and proportion of subjects achieving EASI-50, EASI-75, or EASI-90 in the EASI score will be plotted by treatment and scheduled visits using bar plots. Mean reduction (±SD) from baseline for PP-NRS will be plotted by treatment and study week.

D. Other Efficacy Outcome Analyses

Binary endpoints will be analyzed using similar method as described above for secondary efficacy endpoints:

- EASI-50/EASI-75/EASI-90 at Week 20
- EASI-100 at Week 16 and Week 20
- IGA Score 0
- Proportion of subjects achieving ≥ 2-point improvement in IGA from Baseline to Week 16

- Proportion of subjects achieving ≥ 3-point reduction in weekly average of PP-NRS from Baseline to Week 16, defined for the subset of subjects whose baseline NRS is ≥ 3.
- Proportion of subjects achieving ≥ 4-point reduction in weekly average of PP-NRS from Baseline to Week 16, defined for the subset of subjects whose baseline NRS is ≥ 4.

Continuous endpoints will analyzed using similar method as described above for primary efficacy endpoints, with replacement of each endpoint by EASI in the model; no formal statistical comparison will be performed:

- Change from Baseline to Week 20 in weekly average PP-NRS
- Change in POEM from Baseline to Week 16
- Change in percentage BSA of AD involvement from Baseline to Week 16
- Change in SCORAD from Baseline to Week 16
- Change in DLQI from Baseline to Week 16

AD flares will be recorded as AEs on the eCRF. AD flare related efficacy endpoints will be analyzed using descriptive statistics for each treatment group. Definitions are as follows:

- Number of AD flares from baseline through Week 16
  - defined as the total number of AD flares with an onset date from baseline to Week 16. Number of AD flares will be summarized using descriptive statistics for each treatment group using OC. Number and percentage (along with the 95% CI) of subjects with at least one AD flare during each period will be provided for each treatment group.
- Number of subjects with AD flares from Baseline to Week 8 and from Week 8 to Week 16 and Week 20:
  - AD flares on Baseline to Week 8 and from Week 8 to Week 16 will be defined similarly by AE onset date as described above AD flares that start before Week 8 and are ongoing or resolve after Week 8 will be counted in the first period (baseline to Week 8) only
- Number of days with AD flares through Week 16:
  - the duration of each AD flare is defined as (resolution date of AE – onset date of AE + 1) among subjects with at least one AD flare. For subjects reporting more than one flare, the total subject-days of duration would be calculated and used in statistical summary. Details regarding calculation of duration of AE are described in section 9 below. Number of days with flares will be summarized using descriptive statistics for each treatment group.

All efficacy endpoints will be summarized for FAS using descriptive statistics or frequency counts and percentage for all scheduled visits, for each treatment group.

9. Safety Analyses

Safety analyses will use data from the Safety population. Safety data will be summarized using frequency tables (counts with percentages) and will be presented by treatment and scheduled visits if applicable. Continuous safety data will be summarized using descriptive statistics by treatment and scheduled visits. Data will be compared to the reference ranges provided and be checked for abnormality and/or clinically relevant changes from baseline, where applicable. No formal statistical comparisons will be performed for safety endpoints.

A. Exposure

The following exposure parameters will be defined and summarized by treatment group using descriptive statistics:

- Number and percentage of subjects receiving any injection of study drug at each visit
- Number of injections received at each visit and overall
- Volume (mL) of study drug injected at each visit and overall
- Dose (mg) of study drug injected at each visit and overall
- Number and percent of subjects that have dose interruptions, as well as those with dose interruptions due to AEs

B. Adverse Events

All AEs will be coded using MedDRA version 24.0 or higher. A treatment-emergent AE (TEAE) is defined as any AE that occurs or worsens after initiation of study treatment.

The duration in days of each AE will be calculated as (resolution date of AE – onset date of AE + 1). For the determination of TEAEs and calculation of durations for AD flares, the following rules regarding partial dates will be applied:

- If only the day is missing for a start date, the 1st of the month will be imputed. If the new estimated date falls before the date of first dose, while the known month and year match the month and year of the first dose, the date of first dose will be used as the new estimated date. The AE will be considered as a TEAE.
- If only the day is missing for an end date, the last day of the month will be imputed. If the new estimated date falls after the date of last study visit, the date of last study visit will be used as the new estimated date.
- If both the day and the month are missing for a start date or end date, no imputation will be used, and the duration will not be calculated. However, if the year of start is the same or greater than the year of the first dose date, the AE will be considered as treatment emergent.

- If the start date or end date is completely missing, duration will not be calculated. However, an event with completely missing start date will be considered as treatment emergent.

An overall summary of AEs will be presented by treatment and overall. The summary will include the total number of events, frequency counts and percentages with:

- All AEs
- TEAEs
- Treatment-emergent Serious Adverse Events (SAEs)
- Treatment-related TEAEs
- Treatment-related treatment-emergent SAEs
- TEAEs leading to study drug discontinuation
- Injection site reactions
- AEs of Special Interest (AESIs): conjunctivitis, keratitis and other ophthalmic events evaluated by an ophthalmologist.

Summaries of the incidence of TEAEs will be displayed by treatment according to the following:

- All TEAEs by SOC in descending order of frequency (in the sequence of all subjects, all active treatments, CBP-201 3000 mg [300 mg Q2W] group) and PT in the same order of frequency
- All TEAEs by SOC, PT, and maximum severity (1 mild, 2 moderate, 3 severe, 4 life-threatening, 5 death)
- All TEAEs by SOC, PT, and maximum causality (not related, related) to study treatment
- All serious TEAEs by SOC and PT
- All AESI by SOC and PT

For these summaries, subjects with multiple AEs will be counted only once per SOC and PT.
All AEs will be presented in a by-treatment, and by-subject listing, detailing the verbatim term given by the investigator, the PT, SOC, onset date, end date, CTCAE grade, outcome, relationship to study treatment, action taken with study drug, other action taken, seriousness and criteria for seriousness. SAEs and AEs leading to study treatment discontinuation, and AESI will also be presented in a separate listing.

COVID-19 related adverse events may also be summarized separately if deemed necessary.

C. Clinical Laboratory Results

For continuous laboratory parameters, descriptive statistics will be presented for the value at each assessment time and for the changes from baseline labs by treatment group.

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects in each category will be presented in shift tables.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

D. Vital Signs

Vital signs including sitting blood pressure (systolic and diastolic), heart rate, body temperature and respiratory rate will be presented in a by-subject listing by visit. Descriptive summaries of actual values and changes from Baseline will be calculated for vital signs by treatment group.

E. Electrocardiogram (ECG)

Descriptive statistics will be used to summarize ECG results (actual values and changes from Baseline) at Screening, Baseline (Day 1), and Day 169/Week 24. The incidence of abnormal ECG interpretation will be summarized.

All results will also present in a by-subject listing and abnormal ECG findings will be flagged.

F. Physical Examination

The frequency of subjects with abnormal evaluations of body system findings for physical examinations will be summarized by visit and treatment group. Abnormal physical examination findings will also be presented in a by-subject listing.

Any new findings of Clinically significant abnormalities in physical exam will be recorded as AEs.

G. Injection Site Assessment

The frequency of subjects with any injection site reaction will be summarized by visit and treatment group. Severity (0 to 4) of erythema (0=None, 1=Very Slight, 2=Slight, 3=Moderate, 4=Severe), drainage (0=None, 1=Serous, 2=Serosanguinous, 3=Bloody, 4=Purulent), edema (0=None, 1=Very Slight, 2=Slight, 3=Moderate, 4=Severe), induration (0=None, 1=Minimal, 2=Mild, 3=Moderate, 4=Severe), hematoma (0=None, 1=Minimal, 2=Mild, 3=Moderate,

4=Severe) will be summarized using frequency counts and percentages by visit and treatment group. Injection site reactions will be presented in a by-subject listing.

H. Other Safety Assessments

The frequency of subjects with positive anti-drug antibodies (ADA) will be summarized by visit and treatment group. Positive anti-drug antibodies (ADA) will also be presented in a by-subject listing.

10. Other Assessments

A. PK/PD Analyses

Pharmacokinetics: Individual plasma concentrations will be summarized using descriptive statistics by treatment and scheduled time if applicable or plotted on means overtime if appropriate. The PK analyses will be documented separately in the PK/PD SAP.

Pharmacodynamics: Changes of serum levels of IL-4, IL-13, IgE, TARC and Peripheral eosinophil count will be summarized using descriptive statistics by treatment and scheduled time and, if appropriate, plotted for each treatment together with mean and SD. The PD analyses will be documented separately in the PK/PD SAP. Details and results of the PK and PD analyses will be reported separately in the PK/PD Analytical Report and the PK/PD Report.

11. Changes from the Protocol and Planned Analyses

The following deviations or clarification from the protocol in planned statistical analyses are listed below, along with the justifications:

1. Addition of Week 20 timepoints in Secondary Efficacy Endpoints and Other Efficacy Endpoints in section Secondary Objectives:
   This is to explore the treatment effect after 4 weeks off treatment.
2. The order of testing each CBP-201 group vs. placebo is changed in sections Multiple Comparisons and Multiplicity and Primary Efficacy Outcome Analysis
   From:
   1. After a 600 mg loading dose, 300 mg dose Q2W
   2. After a 600 mg loading dose, 300 mg dose Q4W
   3. After a 600 mg loading dose, 150 mg dose Q2W

   To:
   1. After a 600 mg loading dose, 300 mg dose Q2W
   2. After a 600 mg loading dose, 150 mg dose Q2W
   3. After a 600 mg loading dose, 300 mg dose Q4W

   The decision is based on previous simulated prediction of the CBP-201 concentrations, 150mg dose Q2W group is seen with more potential compared to 300mg dose Q4W group.

3. Using LOCF as the imputation method for primary analysis and WOCF for sensitivity analysis, for primary efficacy and secondary efficacy endpoints. The decision is to allow for comparison of results between the current trial and clinical trials at a similar stage of clinical development for other modalities for atopic dermatitis, for example Thaci et al. 2016 and Guttman-Yassky et al., 2020

12. References

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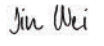
Jin Wei jin.wei@iqvia.com AD, Biostatistics Novella Clinical Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: DB6823E3-3AC7-4EA9-877D-1FB003A64831 Using IP Address: 162.44.245.32 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/15/2021 3:57:54 PM Viewed: 10/15/2021 4:05:13 PM Signed: 10/15/2021 4:05:29 PM
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