Clinical Trial Protocol

Amendment 3: May 28, 2020

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

Investigational Product: CBP-201

IND: 135491

Suzhou Connect Biopharmaceuticals, Ltd

CONFIDENTIAL

PROTOCOL AUTHORIZATION

Title: 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

The study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the guidelines on Good Clinical Practice.

Approved by:

Junying Wang

May 28, 2020

Junying Wang, MD
Medical Science Head

Date

PROTOCOL SIGNATURE PAGE

Title: 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

1. All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), Case Report Forms (CRFs), and scientific data not in the public domain.

2. The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC, except where necessary to avert an immediate hazard to the subjects.

3. I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with all other government, local and regional regulations.

4. I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Reviewed by:

Investigator Name (PRINT)	Research Center
Investigator Signature	Date

1. PROTOCOL SYNOPSIS

Sponsor:	Suzhou Connect Biopharmaceuticals, Ltd. ("Connect") 3rd Floor, East R&D Bldg, Science and Technology Park No. 6 Beijing West Rd. Taicang, Jiangsu, PR China 215400
CRO:	IQVIA Biotech LLC 1700 Perimeter Park Dr. Morrisville, NC 27560
Protocol Number:	CBP-201-WW001
IND#	135491
Study Title:	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
Study Phase:	2
Study Treatment:	CBP-201 is a recombinant monoclonal antibody that binds human interleukin-4 receptor alpha (IL-4Rα), a common subunit of the interleukin 4 (IL-4) and interleukin 13 (IL-13) receptor dimers. CBP-201 blocks signaling from both IL-4 and IL-13 which are thought to play a role in the pathogenesis of atopic dermatitis (AD). CBP-201 is administered as a subcutaneous (SC) injection.
Planned number of Study Sites(s):	Approximately 60
Planned Subject Enrollment	Approximately 220
Indication:	Moderate-to-severe atopic dermatitis
Population:	Adults aged 18 to 75 years, inclusive, who have moderate to severe atopic dermatitis and otherwise meet eligibility criteria may be considered for enrollment into the study.
Study Duration:	Approximately 213 days. • Screening period: up to 45 days • Treatment period: 16 weeks • Follow-up (no dosing) period: 8 weeks
Study Design; Study Treatment Dosing Schedules	This is a randomized, double-blind, placebo-controlled, dose regimen finding study to assess the efficacy, safety, and steady-state PK profile of CBP-201 administered to eligible adult subjects with moderate to severe AD. The

study is divided into a treatment period of 16 weeks and a follow-up period of 8 weeks.

Note that CBP-201 is provided as a single-use 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution of CBP-201 targeted to be approximately 150 mg/mL. Placebo is provided as a single-use 2 mL vial containing 1.2 mL solution without CBP-201. Similar volumes and number of vials are to be used for placebo doses.

Subjects will be randomized 1:1:1:1 into one of the following 4 dosing regimen groups (see in-text table below for a visual representation):

- 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: 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-201 600 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 only: 4 vials on D1, 2 vials on W2 and Q2W thereafter through W16.

CBP-201 or Placebo Treatment Regimen	D1	D15/W2	D29/W4	D43/W6	D57/W8	D71/W10	D85/W12	D99/W14	D113/W16	# Vials over 16 weeks
	Number of vials: C = CBP-201 vs. P = placebo									
600 mg load D1 then 150 mg Q2W	4xC	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	12xC / 8xP
600 mg load D1 then 300 mg Q2W	4xC	2xC	2xC	2xC	2xC	2xC	2xC	2xC	2xC	20xC / 0xP
600 mg load D1 then 300 mg Q4W	4xC	2xP	2xC	2xP	2xC	2xP	2xC	2xP	2xC	12xC / 8xP
placebo	4xP	2xP	2xP	2xP	2xP	2xP	2xP	2xP	2xP	20xP

Note: C = CBP-201; P = placebo; #x = # vials

Using sterile technique, for the CBP-201 300 mg dose, 1 mL is to be withdrawn from each of 2 vials to result in approximately 300 mg CBP-201, and for 600 mg dose, 1 mL is to be withdrawn from each of 4 vials to result in approximately 600 mg. Similarly, for the placebo dose, 1 mL is to be withdrawn from each of 2 vials to result in the equivalent volume to the 300 mg CBP-201 dose, and for 600 mg, 1 mL is withdrawn from each of 4 vials. For the 150 mg CBP-201 dose, in order to maintain the blind, 1 mL is to be withdrawn from each of a CBP-201 vial and a placebo vial to deliver the same volume as a 300 mg CBP-201 dose.

Study Objectives:

Primary objective:

- Assess the efficacy of various treatment regimens of CBP-201 in subjects with moderate to severe AD

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 pharmacokinetic (PK) profile of various treatment regimens for CBP-201 **Exploratory objectives:** In subjects with moderate to severe AD, • Characterize the pharmacodynamic (PD) profile of various treatment regimens for CBP-201 • Characterize the PD/efficacy relationship of various treatment regimens for CBP-201
Eligibility Criteria:	**Inclusion Criteria** A subject must meet the following criteria to be eligible for study participation: 1) Be an adult ≥18 and ≤ 75 years of age at the screening visit (Screening) with atopic dermatitis (according to American Academy of Dermatology Consensus Criteria, Eichenfield 2014, [1]), a) present for at least 1 year prior to the baseline visit (Baseline) with an inadequate response, in the judgement of the Investigator, to AD treatment with a topical regimen of corticosteroids, phosphodiesterase inhibitors or calcineurin inhibitors, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effect or safety risks); b) per Investigator assessment have the following at Screening and Baseline for AD involvement: i. Investigator Global Assessment (IGA) score ≥ 3 (according to Validated Investigator Global Assessment for Atopic Dermatitis [vIGA-AD™] scale, on the 0 to 4 vIGA-AD™ scale, in which 3 is moderate and 4 is severe, see Section 16.4 Appendix D) ii. Eczema Area and Severity Index (EASI) score ≥ 16 (see Section 16.5 Appendix E), and iii. Body Surface Area (BSA) for total AD involvement ≥ 10% (see Section 16.6 Appendix F) 2) Able and willing to apply a stable dose of a bland emollient twice a day to affected areas for at least 7 days before Baseline and to continue for the duration of the study 3) Females of child-bearing potential (FCBP) must abstain from heterosexual activities or agree to use effective contraception. Women who are post-menopausal, as documented by measurement of FSH, or with documented evidence of surgical sterilization prior to Screening. i.e., tubal ligation or hysterectomy are not considered as FCBP. Males who have not undergone a vasectomy must abstain from heterosexual activities

or agree to use effective contraception. All participants must be willing to use effective contraception throughout the entire study period if necessary.

a) Effective contraception options for participating subjects include:

i. Abstinence from sexual intercourse

ii. Using a condom, and a diaphragm or cervical cap, as well as use of a spermicidal (where available)

iii. Oral contraceptives (the "pill") for at least 1 month prior to Baseline

iv. Depo-Provera or injectable birth control or implantable contraception (e.g. Implanon)

v. Intrauterine device (IUD)

4) Able to read and understand, and willing to sign the informed consent form (ICF)

5) Willing and able to comply with clinic visits and study-related procedures

Exclusion Criteria

A subject who meets any of the following criteria will be ineligible to participate in this study:

1) Have any of the following laboratory abnormalities at Screening:

a. Hemoglobin ≤ 90% of the lower limit of normal range (LLN)
b. White blood cell (WBC) below the LLN
c. Neutrophil count below the LLN
d. Platelet count below the LLN

2) Have undergone treatment with any of the following

a. Topical agents such as corticosteroids, phosphodiesterase (PDE) inhibitors, Janus kinase (JAK) inhibitors, tacrolimus or pimecrolimus within 1 week prior to Baseline. Note that low to medium potency topical corticosteroids (TCS) are permitted after randomization to treat AD flares (Section 7.1.2.3)

b. Prior treatment with dupilumab or any antibody against IL-4Rα or IL-13

c. Systemic treatment for AD or other condition with steroids or other immunosuppressive/immunomodulating substances, e.g., cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate or oral Janus kinase (JAK) inhibitors within 4 weeks prior to Baseline. Use of steroid inhalers and nasal corticosteroids is allowed.

d. Cell depleting agents, e.g. rituximab, within 6 months of Baseline or treatment with other biologics within 5 half-lives (if known) or 3 months prior to baseline visit, whichever is longer

	e. Phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), tanning beds, or any other light emitting device (LED), within 4 weeks of Baseline f. ≥ 2 bleach baths within 2 weeks of Baseline g. Prescription emollient to treat AD (e.g. Atopiclair®, MimyX®, Epicerum®, etc.) within 2 weeks of Baseline h. Any investigational drug within 30 days or within 5 half-lives, whichever is longer, before Baseline. i. Live (attenuated) vaccine within 8 weeks of Baseline. j. Treatment with systemic traditional Chinese medicine (TCM) or herbal medications within 4 weeks before Baseline or treatment with topical TCM or herbal medications within 1 week before Baseline visit 3) Have any of the following: a. Infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks before Baseline, or superficial skin infection, such as impetigo, within 2 weeks before the Baseline (subjects may be rescreened after the infection has resolved) b. A history of parasitic infection (e.g. helminth), within 6 months of Baseline c. Per investigator judgement, known or suspected history of immunosuppression within 6 months of Baseline, including a history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, human immunodeficiency virus (HIV), listeriosis, pneumocystosis, or tuberculosis, despite infection resolution; or unusually frequent, recurrent or prolonged infections. d. Any history of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) e. A history of malignancy with the following exceptions: completely treated carcinoma in situ of cervix or non-metastatic squamous or basal cell carcinoma of the skin f. Positive results at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody with positive HCV RNA polymerase chain reaction; positive HIV serology at screening g. An allergy to L-histidine, trehalose or Tween (polysorbate) 80 h. Plans to undergo a major surgical procedure during the study i. Alcohol or drug abuse within 2 years before screening

	j. Any medical or psychiatric condition, laboratory or ECG parameter which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study or interfere with the interpretation of study results 4) Women must not be pregnant, planning to become pregnant or breast-feed during the study.
Study Periods:	**Screening Period (D-45 to D-1)** After providing informed consent, subjects will be assessed for study eligibility at an initial screening visit within 45 days before the baseline visit (Baseline). **Baseline (D1)** Prior to dosing on D1, subjects who have met eligibility criteria during Screening will have eligibility confirmed and undergo baseline assessments and procedures and undergo randomization to scheduled treatments. **Treatment Period (D1 to W16)** Randomized subjects will receive every other week (Q2W) SC injections of CBP-201 or placebo. Subjects will be monitored at the clinical site for 2 hours after the dose administrations on D1, W2 and W4 and 30 min post-dose thereafter. Assessment for adverse events (AEs) and collection of concomitant medications and treatments will be done continuously throughout the study. Treatment with a bland emollient will be done twice daily throughout the study. Subjects may use any bland emollient recommended by the investigator with the cost reimbursed by the Sponsor. Subjects will return to clinic for testing and assessment as described in the Schedule of Events (Table 1). **Follow-up Period (W17-W24)** Subjects will be followed for an additional 8 weeks after the W16 treatments for safety, efficacy and to further characterize the PK and PD profile of CBP-201. Subjects will return to clinic for testing and assessment as described in the Schedule of Events (Table 1). 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. Blood samples will be collected from all subjects throughout the study (see Schedule of Events) to evaluate the CBP-201 steady-state PK profile and PD effects on serum thymus and activation-regulated chemokine (TARC) levels, total immunoglobulin E (IgE) levels, peripheral eosinophil counts and serum

	levels of IL-4 and IL-13. Samples for measurement of antibodies to CBP-201 (anti-drug antibody [ADA], all samples that are positive in the ADA assay will be further tested for the presence of anti-CBP-201 neutralizing antibody [Nab]) will be obtained as described in the Schedule of Events (Table 1).
Screening (D-45 to D-1):	Following signed informed consent, eligibility will be confirmed. Medical history, physical examination (including height and weight), concomitant medication review, clinical laboratory tests, including tests for HIV and hepatitis, and a 12-lead ECG will be obtained during this period. A blood pregnancy test will be obtained for all women of child-bearing potential. AD severity and impact will be assessed as follows: By the investigator: • Investigators Global Assessment (IGA): vIGA-AD™, 5-point categorical scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on the overall appearance of the lesions at a given time point.. • Eczema Area and Severity Index (EASI): EASI score measures 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. The total EASI score ranges from 0 (minimum) to 72 (maximum) points; higher scores reflecting the worse severity of AD. • Percent body surface area (BSA) AD involvement with maximum percentages for each region using the "rule of nines": head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]. The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with AD. The area represented by the palmar surface of the subject's hand with all five digits adducted together, is approximately 1% of the subject's BSA, regardless of the subject's age. Handprints across various body regions assessed is used to calculate BSA % AD involvement. • Severity scoring of AD (SCORAD): a clinical tool for assessing the severity (extent/intensity) of AD and subjective signs/symptoms (e.g. pruritus/insomnia). The extent of AD lesions is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100%. 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). Each item is be scored on the most representative area for a given intensity item. Subjective symptoms are graded using a visual analogue scale (VAS) where 0 = no itch (or insomnia) and 10 = worst imaginable itch (or insomnia). The total score is the sum of extent/5 + 7 x intensity/2 + VAS (symptoms) with a SCORAD range between 0 and 103; higher scores reflecting the worse severity of AD. By the subject:

	• Peak Pruritus Numerical Rating Scale (PP-NRS): an assessment tool that subjects will use to report the maximum itch intensity over the previous 24 hours where 0 = 'no itching' to 10 = 'worst itch imaginable'. See Section 16.1 Appendix A. • Dermatology Life Quality Index (DLQI): a 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. See Section 16.2 Appendix B. • Patient Oriented Eczema Measure (POEM): 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. See Section 16.3 Appendix C. Each assessment or questionnaire is performed at various times during the study as detailed in the Schedule of Events (Table 1) Subjects will also be instructed to apply a bland emollient twice a day to affected areas for the duration of the study (from at least 7 days prior to Baseline to end of study). Subjects may use any bland emollient recommended by the investigator with the cost reimbursed by the Sponsor. All screening laboratory tests will be reviewed by study staff prior to Baseline (D1) to confirm eligibility.
Baseline (D1) Pre-Dosing:	• Confirm eligibility for participation in the study • Review the PP-NRS daily diary for completion, confirmation that a bland emollient has been applied to affected areas for at least 7 days before the baseline visit • AE: query the subject about any AEs occurring during the screening period • Concomitant medications and treatments: query the subject about any new medications or treatments • Efficacy and PROs assessments: per Schedule of Events (Table 1) and at ET, if applicable. Note that PP-NRS score of the maximal itch intensity over the previous 24 hours will be documented in the subject diary for each day, including the visit day. • Perform study assessments and review questionnaires. • Pre-dose: PK, PD, ADA, Safety labs (CBC, chemistry, UA), ECG, urine pregnancy test • Randomization
Treatment Period: Dosing D1 through W16	• AEs: at each visit query subject about any such AEs • Concomitant medications and treatments: at each visit query subject about any new medications or treatments

	• Check prior and current injection site at each visit prior to release from the clinic • Safety labs per Schedule of Events (Table 1) and at ET, if applicable • Trough PK levels and PD assessments per Schedule of Events (Table 1) and at ET, if applicable • ADA per Schedule of Events (Table 1) and at ET, if applicable • Efficacy and PROs assessments: per Schedule of Events (Table 1) and at ET, if applicable. Note that PP-NRS score of the maximal itch intensity over the previous 24 hours will be documented in the subject diary for each day, including the visit day. • Administer study drug and monitor vital signs (VS) • Ensure that clinic discharge criteria are met and review with the subject study requirements and date/time for the next visit
Follow Up Period: W17-W24	• AEs: at each visit query subject about any AEs • Concomitant medications and treatments: at each visit query subject about any new medications or treatments • Check prior injection sites • Efficacy and PROs assessments: per Schedule of Events (Table 1) and at ET, if applicable. Note that PP-NRS score of the maximal itch intensity over the previous 24 hours will be documented in the subject diary for each day, including the visit day. • Safety labs and ECG: W24 • Trough PK, PD and ADA sampling per Schedule of Events (Table 1) • Review with the subject study requirements and date/time for the next visit
Efficacy Outcome Measures:	Per Schedule of Events (Table 1) and at ET, if applicable: • Investigator: IGA, EASI, BSA, SCORAD • Patient-reported outcomes: PP NRS, DLQI, POEM
Safety Outcome Measures:	Adverse events (AEs), AEs of special interest (AE-SI), clinical laboratory evaluations, vital signs, physical examinations including injection site evaluation and concomitant medication/treatment review. Ophthalmic complications are well known to complicated severe AD with incidence rates of 32-56% (2, 3, 4, 5, 6, 7). Nonetheless, conjunctivitis has been a subject of interest in the dupilumab experience. Due to this experience, conjunctivitis and other ophthalmic events should be evaluated by an ophthalmologist and appropriate treatment rendered until resolution.
Mandatory Early Termination from Study Treatment	Using CTCAE Version 5.0 (Common Terminology Criteria for Adverse Events; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf), subjects who develop any related grade 2 or higher cardiovascular or respiratory treatment-emergent adverse events

	(TEAE) or any related grade 3 or higher TEAE involving other organ systems must be discontinued from further study treatment dosing and monitored until resolution or stabilization.
Concomitant Medications:	The following treatments are not permitted, and any use must result in study treatment discontinuation if started after receiving the first dose of study treatment on D1: • Dupilumab or any antibody against IL-4Rα or IL-13 • Topical agents such as phosphodiesterase (PDE) inhibitors, Janus kinase (JAK) inhibitors, tacrolimus or pimecrolimus • Systemic treatment with steroids or other immunosuppressive and/or immunomodulating substances, e.g., cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate or oral Janus kinase (JAK) inhibitors • Cell depleting agents, e.g. rituximab or treatment with other biologic therapeutics • TCM or Herbal medications for AD treatment including topical preparations Use of the following is also prohibited during the study participation: • Allergen immunotherapy • Live (attenuated vaccine) • Phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), tanning beds, or any other light emitting device (LED) • More than 2 bleach baths per week
Treatment of AD Flares:	AD is a chronic relapsing skin condition that is characterized by periods of disease flare or escalation of symptoms. Therefore, when an AD flare occurs, its onset and duration will be documented as an AE by the location(s) of flare involvement. If the Investigator determines that the flare is severe enough to merit "rescue" treatment, document the choice of TCS and instructions for its use and the duration of such permitted rescue TCS treatment. The subject need not be discontinued in this situation. Permitted TCS medications to treat AD flares may include the following: • Cream based preparations or lotion in hair bearing areas • Low to moderate potency TCS (WHO classification VII-IV) equivalent to class VII-IV- according to the U.S classification are allowed. The TCS regimen will be adjusted to the flare activity and tolerability by the subject, and stopped when lesions are cleared. o Examples: ▪ Methylprednisolone acetate 0.1%

	▪ Mometasone furoate 0.1% ▪ Betamethasone valerate cream 0.1% • Any other treatment, topical or systemic is not allowed (apart from bland emollients)
Efficacy Endpoints:	**Primary Efficacy Endpoint:** Comparing each CBP-201 regimen to placebo from Baseline to W16: • EASI-overall: percentage reduction in EASI **Key Secondary Efficacy Endpoints:** Comparing each CBP-201 regimen to placebo: • IGA (0-1): Proportion of subjects with both IGA score 0 to 1 and a reduction of ≥2 points at Week 16 • EASI: o EASI-50: Proportion of subjects achieving ≥ 50% reduction of EASI score from baseline at Week 16 o EASI-75: Proportion of subjects achieving ≥ 75% reduction of EASI score from baseline at Week 16 o 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 of PP-NRS • Number of AD flares from baseline through Week 16 • Number of days with AD flare through Week 16 **Other Efficacy Endpoints:** Comparing each CBP-201 regimen to placebo from Baseline to W16: • Change in POEM • Number of subjects with AD flares (defined as escalation of therapy evidenced by TCS usage) from Baseline to W8 and from W8 to W16 • Proportion of subjects achieving ≥ 2-point improvement in IGA • Change in percent BSA of AD involvement • Change in SCORAD • Proportion of subjects achieving ≥ 3-point reduction in weekly average of PP-NRS • Proportion of subjects achieving ≥ 4-point reduction in weekly average of PP-NRS • Change in DLQI
Safety Endpoints:	Safety will be assessed on basis of: • AEs reported • VS, physical examinations and injection site changes • Safety laboratory parameters, ECG parameters

	• Number (%) of subjects displaying positive anti-drug antibodies (ADA)
Pharmacokinetic (PK) Endpoints:	Whole blood for plasma CBP-201 concentrations will be obtained and analyzed. The individual and treatment regimen group steady-state trough PK profile will be calculated for each treatment schedule. Additional sampling will be obtained after the last treatment dose as noted above to characterize the return to baseline.
Pharmacodynamic (PD) Endpoints:	Changes from Baseline will be summarized with descriptive statistics in serum levels of IL-4, IL-13, IgE, TARC and peripheral eosinophil counts. Additional sampling will be obtained after the last treatment dose as noted above to characterize return to baseline.
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 the treatment effect on the primary endpoint between the CBP-201 300 mg Q2W vs. Placebo. This power calculation is based on the assumptions that the non-inferiority margin of 35% and the significance level is 0.05 two-sided, with the pooled standard deviation of 45%. To further detect the other treatment effects vs. Placebo, and also preserve the alpha at 0.05 level, a hierarchical multiple testing procedure is adopted, from the highest dose (300 mg Q2W) to the lowest dose (150 mg dose Q2W), until statistical significance at 0.05 level is not achieved.
Study Populations; Interim Analyses:	The following six analysis populations are planned for this study: • All Subjects Screened (Screened) set will contain all subjects who signed informed consent. • All Randomized Set (Randomized) will contain all subjects who are randomized into the study, no matter whether they are all treated or not. • The Safety Set (SS) will include all randomized subjects who receive at least part of an SC dose of study treatment. SS will be based on the actual treatment received. • The PK Set (PKS) will include all randomized subjects who receive at least 1 dose of active study treatment, and have at least 1 PK sample collected and analyzable. • The Full Analysis Set (FAS) will include all randomized subjects who receive at least part of an SC dose of study treatment. FAS will be based on the planned treatment (i.e., "as randomized"). • The Per Protocol Set (PPS) will contain a subset of FAS subjects who do not have any major protocol deviations. Study centers, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until final database lock, after the last subject completes the study.

Statistical Methods:	Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate statistical analysis plan (SAP). Descriptive statistics will be used to summarize the safety, PK and PD data. Descriptive statistics will consist of the number of observations, the number of missing observations, mean, standard deviation (SD), standard error, minimum, median, and maximum. Demographic and baseline characteristics will be listed and summarized. Efficacy: The primary efficacy endpoint will be analyzed using the analysis of variance (ANOVA-SAS PROC MIXED procedure) statistical method. Pairwise comparisons for each treatment group vs. placebo will be performed and a serial gatekeeping procedure will be used for multiplicity adjustment. All continuous efficacy endpoints will be summarized using descriptive statistics by treatment group. The categorical efficacy endpoints will be summarized by the number and percentage of subjects for each category, unless specified otherwise. Change from baseline in efficacy endpoints will also be analyzed and graphically presented, if appropriate. Safety: Safety data will be summarized using frequency tables (counts with percentages) and will be presented by treatment and scheduled time, if appropriate. AEs will be classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology. Continuous safety data will be summarized using descriptive statistics by treatment and scheduled time, if applicable. Data will be compared to the reference ranges provided and be checked for abnormality and/or clinically relevant changes from baseline, where applicable. Pharmacokinetics: Individual plasma concentrations will be summarized using descriptive statistics by treatment and scheduled time if applicable or plotted on the means overtime. 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 counts 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.

Table 1: Schedule of Events

Assessments	Screening D-45 to D-1	Baseline pre-dose D1	Treatment Period Visits									Follow-up Period Visits[8]					Unscheduled Visit[16]	Early Termination[16] (+7d)
			Post-dose D1	D15/ W2 (±2d)	D29/ W4 (±2d)	D43/ W6 (±2d)	D57/ W8 (±2d)	D71/ W10 (±2d)	D85/ W12 (±2d)	D99/ W14 (±2d)	D113/ W16 (±2d)	D120/ W17 (±3d)	D127/ W18 (±3d)	D141/ W20 (±3d)	D155/ W22 (±3d)	EOS D169/W 24 (±3d)		
Informed Consent[1]	X	X																
Demographics	X																	
Medical History[1]	X	X																
Eligibility criteria[1]	X	X																
Height	X																	
Body Weight	X	X									X					X		X
Hepatitis & HIV Screens[2]	X																	
Physical Examination[3]	X										X					X	X	X
VS[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X														X		X
Safety Laboratory Tests[5]	X	X		X	X		X				X					X		X
Pregnancy test[6]	X	X					X				X					X		X
PK Blood sample[7]		X		X	X		X		X		X	X	X	X	X	X		X
PD Blood Sample[7]		X		X	X		X		X		X	X	X	X	X	X		X
ADA[8]		X		X	X		X		X		X			X		X		X
Investigator Efficacy Assessments[9]	X	X		X	X		X		X		X			X		X		X

Assessments	Screening D-45 to D-1	Baseline pre-dose D1	Treatment Period Visits									Follow-up Period Visits[8]					Unsched-uled Visit[16]	Early Termina-tion[16] (+7d)
			Post-dose D1	D15/ W2 (±2d)	D29/ W4 (±2d)	D43/ W6 (±2d)	D57/ W8 (±2d)	D71/ W10 (±2d)	D85/ W12 (±2d)	D99/ W14 (±2d)	D113/ W16 (±2d)	D120/ W17 (±3d)	D127/ W18 (±3d)	D141/ W20 (±3d)	D155/ W22 (±3d)	EOS D169/W 24 (±3d)		
Patient Reported Outcomes[10]	X	X		X	X		X		X		X			X		X		X
PP-NRS[11]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug SC Administration[12]			X	X	X	X	X	X	X	X	X							
Apply Bland Emollient[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																
Assess Injection Site(s)[14]			X	X	X	X	X	X	X	X	X	X		X			X	X
Adverse Events[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Meds/Treatments	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AD = Atopic Dermatitis; ADA = anti-drug antibodies; AE = Adverse Event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOS = end of study; FCBP = females of child-bearing potential; HIV = human immunodeficiency virus; HR = heart rate; IGA = Validated Investigator Global Assessment; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetic; PP-NRS = Peak Pruritis Numerical Rating Scale; POEM = Patient oriented eczema measure; Patient reported outcomes = PROs; SAE = serious AE; SC = Subcutaneous; SCORAD = Severity scoring of AD; VS = vital signs

Footnotes:

[1] Informed consent and eligibility confirmation must be reconfirmed on D1 prior to dosing. Medical history also should be reviewed on D1 prior to dosing.

[2] Hepatitis screen: hepatitis B surface antigen or core antibody and hepatitis C antibody.

[3] At screening, Week 16 and EOS/ET, a complete physical examination (PE) will be performed which includes the following: General appearance, skin, eyes/ears/nose/throat, head and neck, heart, lungs, abdomen, extremities, lymph nodes, musculoskeletal and neurologic. A rectal or genital examination is not required unless necessary to assess for AD involvement. Focused PE can be completed at visits when a schedulerd PE is not done, with attention to areas affected by atopic dermatitis and to evaluate any AEs.

[4] VS includes body temperature, respiratory rate, BP, HR. On dosing days, VS should be done pre-dose and hourly during the 2-hour post-dose monitoring period on D1, W2 and W4, and at 30 min post-dose for W6 and beyond. During the follow up period, VS are to be done once during the visit.

[5] Clinical lab assessments: see Table 4. If the screening safety lab test is within 7 days of Baseline visit, the labs do not need to be repeated at Baseline visit. Labs should be drawn pre-dose if on a treatment day.

[6] All FCBP will be tested for pregnancy by a blood pregnancy test at Screening and by urine pregnancy test at Baseline and Q8W thereafter. If the screening test is within 7 days of Baseline visit, the Pregnancy Testing does not need to be repeated.

[7] Trough PK/PD samples should be collected prior to each treatment dose (D1, W2, W4 and Q4W thereafter to W16); date and clock time for each sample will be recorded. After the subject comples the treatment period with the final study treatment dose on W16, additional PK samples will be obtained on W17, W18 W20, W22, and W24.

[8] On the days that ADA is to be drawn, the ADA sample can be taken from PD sample. A separate sample for ADA assessment does not need to be drawn. Also ensure that the sample is large enough for Nab analysis if ADA is positive
[9] Assessments/procedures should be conducted in the following order: Patient reported outcomes (PROs), Investigator assessments, safety and laboratory assessments, and then administration of the study drug. Pre-dose Investigator assessments include EASI, IGA, BSA, and SCORAD. Investigator assessments should be performed by the same person for a single subject, when possible.
[10] Pre-dose Patient Reported Outcomes includes PP-NRS, DLQI, and POEM. However, PP-NRS is included as a separate row in the SoE since completion of this diary has a different schedule
[11]The PP-NRS (daily itch diary) will be distributed at start of Screening and will be reviewed by study staff at the Baseline Visit (D1). PP-NRS must be completed at Screening, and a daily diary for subject completion for the 7 days prior to the Baseline Visit to establish their pre-treatment itch intensity baseline and, during the study, the PP-NRS score of maximal itch intensity over the previous 24 hours will be documented in the subject diary for each day.
[12] Subjects are to remain for 2 hours post-dose for D1, W2, and W4 and 30 min post dose from W6 on; assessments and testing should be completed pre-dose except as otherwise noted. Rotate injection sites: abdomen [avoid area proximal to umbilicus], outer thigh, upper arm [lateral or posterolateral].
[13] Instruct subject to apply bland emollient twice daily to affected areas starting 7 days prior to the Baseline Visit to the study completion visit. To allow for assessment of dryness and scaling, emollients should be avoided during the 4 hours prior to evaluation. Subjects may use any bland emollient recommended by the investigator and the cost will be reimbursed by the Sponsor.
[14] The SC injection site will be assessed using a standard instrument that will be provided to each study site for evaluating injection site findings. Clinically significant findings as determined by the Investigator will be reported as an AE. On dosing days, the previous injection site(s) (except on D1) should be assessed prior to dosing and the new injection site should be assessed prior to release.
[15] AEs and SAEs will be collected starting from the time that the Informed Consent is signed. AEs and AEs of special interest (AESIs) will be collected at each study visit. During follow-up period beyond study completion or after an ET, only those SAEs considered to be related to study treatment should be reported.
[16] Unscheduled or early termination (ET) visits may occur at any time. Unscheduled visits (UVs) may occur to assess AEs or disease progression, for example. It is left to Investigator discretion to determine what if any assessments are appropriate for an UV, however VS, physical examination, assessment of injection sites, query subject for any AEs and new concomitant medications or treatments at the minimum should be performed. UVs occurring after W24 may be scheduled to follow AEs to resolution or establishment of a new baseline (progression of AE has been stabilized) or for assessments regarding disease progression. After an ET, a visit should be scheduled promptly to determine the reason for ET and to perform study closeout assessments assuming the subject is willing to return to the clinic and undergo such procedures. Note that subjects who develop any CTCAE grade 2 or higher cardiovascular or respiratory TEAE or any grade 3 or higher TEAE involving other organ systems must be discontinued from further study treatment dosing and monitored until resolution or stabilization.

2. SUMMARY OF CHANGES

In addition to the changes described below, administrative changes for style, grammar, spelling, interpretability, clarification and consistency have been made as applicable in the document.

Changes made throughout this protocol are as noted below:

- Title of protocol was changed to delete reference to "double-dummy"
  Rationale: The term is not fully accurate, as no true double-dummy design is incorporated
- Title of protocol was changed to delete reference to "repeated dose"
  Rationale: The term is not necessary to include and is somewhat redundant to design
- Title of protocol was changed to change reference of "patients" to "adult subjects"
  Rationale: The term "subjects" is otherwise used throughout the protocol, rather than "patients" and "adult" is added for additional clarity
- IND Number is added
  Rationale: Information had become available to add to protocol
- Sponsor Company Name is updated as necessary throughout
  Rationale: To correct inconsistent use of name
- "Reviewed By" field is removed from Protocol Authorization page
  Rationale: Inclusion was determined to be unnecessary
- "Approved By" signature is updated
  Rationale: Chief Medical Officer position is currently vacant, and CEO is signing for approval
- The optional blinded treatment extension is removed, along with references and associated activities throughout protocol
  Rationale: The blinded extension was determined to add little or no value to the key data collection nor to assessment / achievement of key study endpoints
- Amendment of Previous Sample Size Justification section.
  Rationale: the previous power and sample size calculation was based on empirical. With preliminary results at week 4 and more empirical data, nuisance parameters like standard deviation and treatment effect can be more estimated.
- Inclusion Criterion #1 is amended to allow the moderate to severe AD subjects for whom topical treatments are medically inadvisable to be enrolled into this study
  Rationale: To enable the study to assess the efficacy and safety in moderate to severe AD subjects for whom topical treatments are medically inadvisable. According to the clinical guideline, this part of patient population may benefit from Biologics treatment. In addition, based on the mechanism of CBP-201 and the preliminary efficacy data of CBP-201, CBP-201 treatment may prove to be beneficial to moderate to severe AD subjects for whom topical treatments are medically inadvisable

- Specific diagnosis criteria of atopic dermatitis is added to the inclusion criteria #1.
  Rationale: To specify American Academy of Dermatology Consensus Criteria, Eichenfield 2014 will be used to confirm the diagnosis of AD in this study.
- Amendment of inclusion criteria #1 for Eczema Area and Severity Index (EASI) score: adjusted the cut-off value of EASI score at Screening and Baseline visits from 12 to 16
  Rationale: The adjustment of the cut-off value of EASI score at Screening and Baseline visits will ensure the study target patient population to be more consistent with the clinical guideline with respect to the biologic-eligible AD patient
- Inclusion Criterion #1 is updated to add further explanation of Investigator Global Assessment (IGA) score
  Rationale: To clearly define Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD™) would be used in this study, matching licensed requirements for naming of tool, and to provide clarification of the IGA scores
- Inclusion criteria #3 was updated to remove the time limitation of surgical sterilization prior to screening for women
  Rationale: Women with documented evidence of surgical sterilization at any time prior to Screening should not be considered Females of child-bearing potential (FCBP). The requirement of having had surgical sterilization at least 6 months prior to screening is unnecessary
- The required washout period for Topical agents, systemic treatment for AD and other biologics apart from cell depleting agents are updated in Exclusion criteria #2
  Rationale: Required washout period prior to Baseline for treatment agents above are updated in accordance to their pharmacokinetic characteristics
- Washout periods for systemic and topical traditional Chinese medicine (TCM) or herbal medications were added to exclusion criteria #2
  Rationale: Concomitant treatment of systemic or topical traditional Chinese medicine (TCM) or herbal medications may interfere with study efficacy and safety assessments
- Prohibition of oral and parental antibiotics, antivirals, or systemic antifungals within 8 weeks prior to Baseline in exclusion criteria #2 is moved to exclusion criteria #3 and is amended
  Rationale: To further clarify the subjects with infections requiring treatment with systemic anti-infective agents within 4 weeks before the Baseline will be excluded
- Exclusion criteria #3 about vernal conjunctivitis is amended
  Rationale: To exclude the subject with any history of vernal keratoconjunctivitis (VKC) and Atopic keratoconjunctivitis (AKC) for patients' safety because these diseases are recurrent or chronic allergic inflammatory disease of the ocular surface
- Exclusion criteria #3 about viral serology screening is updated
  Rationale: To exclude the subject with positive HIV serology at screening
- Exclusion criteria #3 is amended to exclude subjects with alcohol or drug abuse within 2 years before screening
  Rationale: Recent history of Alcohol or drug abuse may make a subject's participation unreliable

or may interfere with study assessments

- Included statement regarding analysis of neutralizing antibodies in cases where anti-drug antibody assessment is positive
  Rationale: Was not previously noted in the protocol
- Replacement of the SCORAD scale used for the study
  Rationale: The licensed image is not an adult. Even though the image is an adolescent/child, the licensed image will now be used
- Pruritis Numeric rating Scale (P-NRS) is updated to now use validated Peak Pruritis Numeric Rating Scale (PP-NRS)
  Rationale: To match the licensed version
- Amendment of Early Termination (ET) visit to specify additional posttreatment follow-up period visits should be requested for ET subjects if appropriate and to add the definition of subjects lost to follow-up.
  Rationale: To ensure the ET subjects will be followed up appropriately. To highlight all reasonable efforts must be made to contact the subjects for subjects who fail to return to sites.
- Update AE/SAE causality discussions to eliminate "unlikely", "possibly" and "probably" and only retain "related" or "not related"
  Rationale: Simplify and align with CDISC
- Update AE/SAE collection periods to include any AEs/SAEs occurring from the time of subject signing of Informed Consent through the end of study
  Rationale: Collection periods were previously inconsistent between AE and SAE, and updated intent to collect both types of Aes similarly
- Added text to "SAE Collection" section to include collection of any SAEs after the end of the study period which have a reasonable possibility, in the opinion of the investigator, of being related to the investigational drug
  Rationale: Ensure collection of SAEs that have a potential to be related to the investigational drug after the end of the study
- Amendment of AD flare and rescue treatment to add specific instructions and recommendations about the rescue treatment for AD flare
  Rationale: Due to the potential impact of rescue treatment on efficacy assessment, this section is amended to further clarify the permitted rescue TCS for AD flare treatment, and specify that the initiation of any other rescue treatment including other topical rescue treatments, systemic rescue treatment would lead to the study treatment discontinuation.
- Added TCM or Herbal medications, allergen immunotherapy and live (attenuated vaccine), etc. to the prohibited concomitant treatment
  Rationale: Concomitant treatment of TCM or herbal medications, allergen immunotherapy, etc. may interfere with study efficacy and safety assessments

- Change the wording of some secondary study endpoints and add "Proportion of subjects achieving ≥ 4-point reduction in weekly average of PP-NRS" as an efficacy endpoint
  Rationale: For clarification and consistency.
- Added "peripheral eosinophil counts" to PD assessment description
  Rationale: Was previously inadvertently not included
- Added to footnote of Table 1 and in protocol body with relation to Physical Exam that if subjects have any symptom or sign of ocular surface diseases, e.g., conjunctivitis and blepharitis, at screening or during study period, the subject should be evaluated by ophthalmologist.
  Rationale: Was previously inadvertently not included.
- Added text to "AD Flares" section to address rescue treatment descriptions
  Rationale: Was previously not included.
- "Study Restrictions" section was updated to include several items
  Rationale: To be consistent with the changes made in the concomitant medication section.
- "Study Treatment Accountability" section was updated to allow for on-site destruction (at clinical trial sites) of investigational drug
  Rationale: To simplify investigational drug management
- "Treatment Compliance" section was amended
  Rationale: To clarify how accountability of investigational drug will be managed and also to clarify that subjects will not have direct access to investigational drug.
- Section for "Height and Body Weight" was added
  Rationale: To help clarify when these assessments are made
- "Physical Exam" section was amended
  Rationale: To include reference to management of ocular surface findings.
- Amendment of Pregnancy section.
  Rationale: To clarify the pregnancy report procedure and follow up requirement. To Specify the pregnancy outcomes that should be considered as SAEs and that should follow the SAEs reporting procedure
- Removed requirement for replacing subjects who had discontinued or had been discontinued prior to completion of Week 4
  Rationale: It is determined that the enrollment plan negates this requirement, as enough subjects will be enrolled to allow for appropriate analysis of collected data
- Amendment of Previous Human Experience section regarding Study CBP-201AU002
  Rationale: To supplement with the currently available results from Study CBP-201AU002
- Amendment of Missing data section
  Rationale: To correct that subjects without efficacy data at a specific time point will be considered as non-responders is applicable for analysis of binary efficacy endpoints.

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
AESI	AE of special interest
AKC	Atopic keratoconjunctivitis
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
AUC_{last}	Area under the curve at the last time point
BLQ	Below limit of quantitation
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum plasma concentration
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract research organization
CS	Clinically significant
D# or D-#	Day # (study days), Day -# (prior to treatment start)
DBP	Diastolic Blood Pressure
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Scale
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ET	Early Termination
FCBP	Female of child-bearing potential
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice

Abbreviation	Term
H	Hours
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Validated Investigator Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IL-13	Interleukin-13
IRB	Institutional Review Board
ISR	Injection Site Reaction
LDH	Lactate dehydrogenase
mAb	Monoclonal antibodies
MDC (CCL22)	Human macrophage-derived chemokine
mcg or μ	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minutes
mL	Milliliter
Nab	Neutralizing Antibody
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PE	Physical examination
PI	Principal Investigator
PK	Pharmacokinetic
P-NRS	Pruritis Numeric Rating Scale
POEM	Patient Oriented Eczema Measure
PP-NRS	Peak Pruritus Numeric Rating Scale (0-10) over the past 24 hours
PPS	Per protocol set
PRO	Patient reported outcome
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Term
SBP	Systolic blood pressure
SC	Subcutaneous
SCORAD	Severity Scoring of AD
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SRC	Safety review committee
SS	Safety set
SUSAR	Suspected unexpected serious adverse reaction
T#	Time (hours)
$t_{½}$	Elimination half-life
TARC (CCL17)	Thymus activation regulated chemokine
TCM	Traditional Chinese medicine
TCS	Topical corticosteroids
TEAEs	Treatment emergent adverse event[s]
TEAE-SI	Treatment emergent adverse event[s] of special interest
T_{max}	Time to maximum plasma concentration
US	United States
V	Volume of distribution
VKC	Vernal keratoconjunctivitis
W#	Week # visit after treatment start
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects millions of patients worldwide. AD usually presents in childhood, most commonly in infancy with two-thirds presenting by age 2 years, but AD also may be delayed until later in life (8). However, a recent hospital-based study in China reported that out of 2662 patients, 77.5% had onset of disease after 12 years of age (9). It affects 15%-20% of children (8) but is seen less commonly in adults (point prevalence 1.6-11.5% but with wide variability from country to country) (1, 10). Among other bothersome symptoms, AD is characterized by intense pruritis and recurrent eczematous skin lesions (11). Sleep disturbance, unrelenting pruritis and social embarrassment can lead to depression and other psychological disturbances (12, 13, 14, 15, 16).

The pathophysiology of AD is complex and involves an interplay of skin barrier function, genetics, environmental factors and immune responses. Skin barrier function in AD is reduced and transdermal water loss is increased. Localized inflammation and trauma from scratching can lead to further breakdown in barrier function and infection (17, 18, 19, 20). A family history of atopy is strongly associated with development of AD, as are loss of function mutations in the filaggrin gene (21). With respect to the immunologic disturbances, excessive T-cell activation with infiltration of the skin by T-cells and dendritic cells is a hallmark of AD (20). T-helper cytokines including interleukin (IL)-4, IL-5, IL-13 and IL-31 have been linked to the pathophysiology of AD (22). Therapy directed against cytokines is an area of active research and drug development (23).

Diagnosis of AD is made on clinical grounds and guidelines for diagnosis, such as the Hanafin and Rajka criteria, have been utilized in clinical and research settings (1). The Hanafin and Rajka criteria require a combination of major criteria (e.g. pruritis, chronic dermatitis and history of respiratory/cutaneous allergy) and minor criteria (e.g. facial pallor, infraorbital darkening, environmental or food triggers) to establish the diagnosis of AD. No specific laboratory or tissue histopathologic findings have been identified, but AD is sometimes associated with elevated immunoglobin E levels and eosinophilia (24, 25, 26).

Topical agents, such as moisturizers, emollients and corticosteroids are commonly used for treatment of AD (27). Other topical treatments include calcineurin inhibitors such as tacrolimus, antibiotics and phosphodiesterase inhibitors (28). There are limitations to the use of topical agents such as limited efficacy, application site reactions, application site restrictions and concerns about complications of long-term use (steroids, calcineurin inhibitors) (29). Systemic therapies include antibiotics, steroids, cyclosporine, methotrexate, and others, however, inadequate efficacy as well as safety concerns such as adrenal suppression, Cushing's Syndrome, organotoxicity and cancer risk are important limitations of available systemic therapy (30, 31, 32). Dupilumab, a mAb directed against IL-4 receptor alpha, was approved in the US for

treatment of moderate to severe AD in adults (2017) and adolescents (2019) when disease is not adequately controlled by topical therapies and is similarly approved in other countries as well (33, 34, 35). See also, Dupixent® (dupilumab) Official HCP website (36).

CBP-201 is a human IgG4 kappa monoclonal antibody directed against IL-4 receptor alpha. As with dupilumab, CBP-201 blocks signaling from both IL-4 and IL-13, which are thought to play a role in the pathogenesis of AD. Preclinical work has demonstrated that CBP-201 has a desirable pharmacologic profile with high affinity and specificity for the target with greater potency and a longer half-life relative to dupilumab. CBP-201 is being developed for treatment of AD initially, with plans to develop in other indications such as asthma and other inflammatory conditions.

5.2. Physical, Chemistry and Pharmaceutical Properties

The CBP-201 is recombinant human monoclonal antibody that binds human interleukin-4 receptor alpha (IL-4Rα), a common subunit of the interleukin 4 (IL-4) and interleukin 13 (IL-13) receptor dimers. It is a human IgG4 containing a kappa light chain, with a predicted protein molecular weight of approximately 144 kDa. The amino acid Ser223 in the Fc region in the heavy chains has been mutated to Pro223 to promote stabilization of the molecule.

CBP-201 drug product is supplied as a clear to slightly opalescent, colorless to pale yellow liquid solution. The containers are 2 mL glass vials each containing 1.2 mL of 150 mg/mL of CBP-201 drug substance in sterile solution for administration. The formulation of the CBP-201 solution contains excipients including L-histidine, NaCl, Trehalose, and Tween 80. The placebo control solution contains the same excipients without the CBP-201 drug substance.

5.3. Preclinical Results

Preclinical data demonstrates that CBP-201 has a desirable pharmacologic profile, including a high affinity and specificity for the antigen resulting in greater potency and a longer half-life when compared to dupilumab. Extensive *in vitro* studies characterizing the pharmacological properties of CBP-201 are reported. CBP-201 has a very high affinity for soluble recombinant Human IL-4Rα and inhibits the proliferation of erythroleukemic (TF-1) cells. CBP-201 also inhibits IL-4- and IL-13-mediated signal transducer and activator of transcription 6 (STAT6) activation in Human embryonic kidney (HEK) -Blue™IL-4/IL-13 SEAP cells. In *ex vivo* assays, CBP-201 inhibits IL-4- and IL-13-induced production of the chemokine thymus and activation regulated chemokine (TARC, also known as CCL17) and MDC (Human macrophage-derived chemokine [CCL22]) in Human peripheral blood mononuclear cells. These studies demonstrate CBP-201 is a high affinity antibody for IL-4Rα. The PK properties of CBP-201 have been studied in mice and monkeys with excellent dose proportionality observed across three dose levels, indicating good bioavailability.

Similar to other drugs in the same class (e.g., dupilumab), CBP-201 does not cross-react with IL-4Rα in preclinical species (mice, rats, monkeys). As such it was not possible to directly assess the toxicity of IL-4Rα inhibition by CBP-201 in animals. Connect conducted a 4-week toxicology study in monkeys to assess the potential off-target toxicity of CBP-201 to support a single dose FIH study in healthy volunteers. In this study 4 weekly SC injections of CBP-201 into cynomolgus monkeys at 6, 40 and 200 mg/kg were well tolerated. The no observed adverse effect level (NOAEL) of CBP-201 was 200 mg/kg, which corresponds to a C_{max} of approximately 6279 µg/mL and an area under the time concentration curve to the last measurable concentration (AUC_{last}) of approximately 837.4 h*mg/mL at the last dose. There were no clinically meaningful changes in clinical observations, macroscopic observations, coagulation, clinical chemistry, hematology, lymphocytes changes, plasma complement and cytokine levels in the study.

5.4. Previous Human Experience

5.4.1. Study CBP-201AU001

A first-in-human single ascending dose study (Protocol CBP-201AU001) entitled "A Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CBP-201 Administered to Healthy Adult Subjects" has been completed (CSR CBP-201AU001). This was a single center, randomized, double-blind, placebo-controlled single ascending dose (SAD) study to assess the safety, tolerability, PK and PD profile of CBP-201 administered subcutaneously (or IV for cohort 5) to healthy adults aged 18-65 years, inclusive, who met all eligibility criteria. The study enrolled 5 cohorts of subjects who were randomized to receive a single dose of CBP-201 or placebo. Each cohort enrolled 8 subjects, of which 6 received active investigational product (IP) and 2 received placebo. Sentinel subjects (1 active:1 placebo) were used in Cohort 1 and for all dose escalations. Cohorts 1 through to 4 were administered study drug via the SC route. Cohort 5 subjects received their assigned treatment via IV administration.

The initial dose (Cohort 1) was a single administration of CBP-201 75 mg (or matching placebo). A sequential dose escalation (Cohorts 2-4) and additional cohort (Cohort 5) CBP-201 300 mg (or matching placebo) administered IV followed. Interim safety reviews by a Safety Review Committee (SRC) prior to proceeding to the next cohort were conducted. The dose levels per Cohort were as follows:

Cohort 1: 75 mg or matching placebo via SC administration

Cohort 2: 150 mg or matching placebo via SC administration

Cohort 3: 300 mg or matching placebo via SC administration

Cohort 4: 600 mg or matching placebo via SC administration

Cohort 5: 300 mg or matching placebo via IV administration

The study consisted of a Screening Period (up to 30 days), a Baseline Visit (Day -1 to 1), and nine additional follow-up visits over the following 85±2 days. Study drug or placebo was administered on Day 1. Subjects remained in the clinical center for 24 hours post-injection to monitor for any local injection site reactions, record adverse events (AEs), assess vital signs (VS) and perform post-injection 12-lead electrocardiogram (ECGs), and to collect blood for PK and PD analysis. Subjects were discharged from the clinic on Day 2. Follow-up visits were conducted on Days 4, 8, 11, 15, 22±2 days, 29±2 days, 43±2 days, 57±2 days and 85±2 days. The final planned study visit occurred on Day 85±2.

A total of 108 adult subjects were screened and 40 were enrolled and randomized with 39 completing the study per protocol and one subject who was lost to follow-up. CBP-201 appeared to be safe and well tolerated when administered to healthy male and female adult volunteers at SC doses from 75 mg up to 600 mg and following 300 mg administered IV. These conclusions were based on the following findings from all 40 treated subjects:

- There were no SAEs, life-threatening TEAEs or deaths reported on study.
- There were no TEAEs leading to discontinuation from the study.
- The majority of TEAEs were mild, 16 of the 86 (18.6%) TEAEs that occurred were moderate and there were no severe TEAEs. The severity of TEAEs and treatment-related TEAEs did not increase with increasing CBP-201 dose level nor was severity of TEAEs associated with a particular route of administration (SC compared to IV delivery).
- The incidence of TEAEs and treatment-related TEAEs was equivalent or lower for CBP-201-treated subjects compared to placebo-treated subjects and did not increase with increasing CBP-201 dose level. Across all treatment groups, 31 out of 40 subjects reported at least 1 TEAE, 24 (80.0%) of which were treated with CBP-201 and 7 (70.0%) of which received placebo. Across all treatment groups, 16 out of 40 subjects reported at least 1 treatment-related TEAE, 11 (36.7%) of which received CBP-201 and 5 (50.0%) of which received placebo
- The most common TEAEs and treatment-related TEAEs were headache and upper respiratory tract infection (URTI), which occurred with similar frequency in the All CBP-201 and All Placebo groups.
- There were no clinically significant and/or study drug-related changes in vital signs, ECG parameters, or physical examination findings. Two (2) injection site reactions (ISRs) occurred in 2 SC CBP-201 treated subjects which were reported as AEs. There were no ISRs reported as AEs for subjects receiving placebo. Both were deemed to be mild in severity and resolved. Injection site reactions did not occur with 300 mg IV administration of CBP-201. Regardless of treatment assignment or SC CBP-201 dose level administered, there were no occurrences of injection site reactions greater than Grade 1.

Pharmacokinetics: The exposure to CBP-201 after SC administration increased in a dose-related but greater than dose-proportional manner, suggesting a nonlinear component to clearance. Comparing 300 mg SC and IV doses, the absolute bioavailability after SC administration was 58% and the median time to last detectable drug ranged from 338 hours at 75 mg to 1345 hours at 600 mg.

Pharmacodynamics: Single SC doses of 75 mg to 600 mg of CBP-201 significantly reduced plasma TARC levels. Comparable decreases are observed for all four SC doses and for the IV dose. Overall, the relationship between the percent change in TARC and plasma CBP-201 was relatively flat across the range of plasma concentrations in this small single dose study.

5.4.2. Study CBP-201AU002

A follow-on study (Protocol CBP-201AU002) entitled: "A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of the Safety, Pharmacokinetics and Preliminary Efficacy of CBP-201 in Patients with Moderate to Severe Atopic Dermatitis" has been completed (Clinical Study Report is still in the process of development) at the time of this protocol. This study is a 12-week, double-blind, randomized, placebo-controlled, multi-center, multi-national, multiple ascending dose (MAD) study to assess the safety, PK profile and preliminary efficacy of treatment with CBP-201 in subjects with moderate to severe AD. The primary objective of this study was to assess the safety and tolerability of multiple subcutaneous (SC) doses of CBP-201 in patients with moderate to severe AD.

This study was conducted at 9 study sites in Australia and 4 in New Zealand. Subjects were randomized in a 4:1 ratio to receive CBP-201 or placebo once a week for 4 doses, with approximately 10 patients (8 active:2 placebo) randomized in each dose cohort. Three ascending dose levels were planned (75, 150 and300 mg CBP-201). All dose escalations were subject to Safety Review Committee blinded review. The treatment period was 4 weeks in duration. Subjects were followed for an additional 8 weeks for safety, efficacy and to further characterize the PK and PD profile of CBP-201.

A total of 86 subjects were screened and 32 subjects with moderate to severe AD (ages 20 – 65) were enrolled and randomized with 31 completing the study and one subject who was withdrawn from the study on Day 1 following randomization but prior to dosing. The study results are listed as following:

Efficacy: Administration of CBP-201 for 4 weeks resulted in rapid improvements in EASI, IGA, and Pruritis Numeric Rating Scale (P-NRS) at all doses above the lowest dose (75 mg). On Day 29, 87.5% (7/8) of patients in the 150mg group had a 50% reduction in the EASI score (EASI-50) while 100% (7/7) of patients in the 300 mg group achieved EASI-50 versus 37.5% (3/8) in the placebo group. For IGA, 50.0% (4/8) of patients in the 150 mg group, 42.9% (3/7) of patients in the 300 mg group, and only 12.5% (1/8) in the placebo group had an IGA score of 0 to 1 (clear, almost clear). Average weekly P-NRS in severity decreased by 41.0% in the CBP-201

150 mg group, by 52.8% in the 300 mg group versus 22.8% in the placebo group. P-NRS response rates (>3-point decrease) were greater for the 150 mg (50%, 4/8) and 300 mg groups (57%, 4/7) versus the placebo group (25%, 2/8) on Day 29.

Safety: CBP-201 appeared to be safe and well-tolerated when administered to male and female adult patients with moderate to severe AD, at SC doses of 75 mg, 150 mg, and 300 mg. These conclusions were based on the following findings from 23 patients in the pooled CBP-201 group who received at least one dose of CBP-201 and 8 of 8 patients in the placebo group.

- There were no SAEs, life-threatening TEAEs, or deaths reported on study.
- There were no TEAEs leading to the discontinuation from the study.
- The majority of TEAEs were mild. The number and severity of TEAEs and treatment related TEAEs did not increase with increasing CBP-201 dose level. Of 51 TEAEs reported across the pooled CBP-201 group, 9 events were deemed by the Investigator to be related to study drug, and 3 of 11 TEAEs in the placebo group were deemed related to placebo treatment. There was no treatment related severe TEAEs reported.
- The most common Adverse Events (AE) during the study were exacerbation of AD (26.1% in the combined CBP-201 group and 37.5% in placebo group), headache, and upper respiratory tract infection.
- By dose across the CBP-201 treatment groups, there were no apparent differences between the different dosing groups in terms of study treatment related TEAEs.
- There were no clinically significant injection site reactions that were reported as AEs
- There were no clinically significant and/or study drug-related changes in vital signs, ECG parameters, or physical examination findings.
- Immunogenicity assay results showed 5 of 23 patients (21.7%) had a treatment-induced positive response for ADA with very low titration. Overall, the immunogenicity of CBP 201 varied inversely with the CBP-201 dose, with the incidence of treatment-induced ADA positive response observed to decrease with greater CBP 201 doses.

Pharmacokinetic: The highest CBP-201 concentrations were observed approximately one week (Day 29) after the fourth CBP-201 administration on Day 22. The median t1/2 was approximately 10 days for the CPB-201 150 mg to 300 mg groups. Dose proportionality assessed based on $AUC_{0\text{-}t}$ and C_{max}, showed that an increase in exposure was greater than proportional as the dose increased from 75 mg to 150 mg, and proportional when the dose increased from 150 mg to 300 mg.

Pharmacodynamics: CBP-201 at the 150 mg and 300 mg doses resulted in a steady decline of serum TARC and LDH.

5.5. Study Rationale

CBP-201 is a recombinant monoclonal antibody that binds human interleukin-4 receptor alpha (IL-4Rα), a common subunit of the interleukin 4 (IL-4) and interleukin 13 (IL-13) receptor dimers. CBP-201 blocks signaling from both IL-4 and IL-13 which are thought to play a role in the pathogenesis of atopic dermatitis (AD). CBP-201 is administered as a subcutaneous (SC) injection. This study is designed to test various CBP-201 dosing regimens over an extended period in subjects with AD.

6. STUDY OBJECTIVES

6.1. Primary Objective

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

6.2. 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 pharmacokinetic (PK) profile of various treatment regimens for CBP-201

6.3. Exploratory Objectives

Exploratory objectives of the study are: In subjects with moderate to severe AD:

- Characterize the pharmacodynamic (PD) profile of various treatment regimens for CBP-201
- Characterize the PD/efficacy relationship of various treatment regimens for CBP-201

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a 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.

Subjects will be randomized 1:1:1:1 into one of the following 4 dosing regimen groups (Table 2):

- 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: 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-201 600 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 only: 4 vials on D1, 2 vials on W2 and Q2W thereafter through W16.

Table 2. Subcutaneous Injection Schedule Through Week 16

CBP-201 or Placebo Treatment Regimen	D1	D15/W2	D29/W4	D43/W6	D57/W8	D71/W10	D85/W12	D99/W14	D113/W16	# Vials over 16 weeks
	Number of vials: C = CBP-201 vs. P = placebo									
600 mg load D1 then 150 mg Q2W	4xC	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	1xC / 1xP	12xC / 8xP
600 mg load D1 then 300 mg Q2W	4xC	2xC	2xC	2xC	2xC	2xC	2xC	2xC	2xC	20xC / 0xP
600 mg load D1 then 300 mg Q4W	4xC	2xP	2xC	2xP	2xC	2xP	2xC	2xP	2xC	12xC / 8xP
placebo	4xP	2xP	2xP	2xP	2xP	2xP	2xP	2xP	2xP	20xP

Note: C = CBP-201; P = placebo; #x = # vials.

Using sterile technique, for the CBP-201 300 mg dose, 1 mL is to be withdrawn from each of 2 vials to result in approximately 300 mg CBP-201, and for 600 mg, 1 mL is to be withdrawn from each of 4 vials to result in approximately 600 mg. Similarly, for the placebo dose, 1 mL is to be withdrawn from each of 2 vials to result in the equivalent volume to the 300 mg CBP-201 dose, and for 600 mg, 1 mL is withdrawn from each of 4 vials. For the 150 mg CBP-201 dose, in order to maintain the blind, 1 mL is to be withdrawn from each of a CBP-201 vial and a placebo vial to deliver the same volume as a 300 mg CBP-201 dose.

7.1.1. Screening Period (Day -45 [D-45] to D-1):

After providing informed consent, subjects will be assessed for study eligibility at an initial screening visit within 45 days before the baseline visit. Medical history, physical examination

(including height and weight), concomitant medication review, clinical laboratory tests, including tests for HIV and hepatitis, and a 12-lead ECG will be obtained during this period. A blood pregnancy test will be obtained for all women of child-bearing potential.

See Table 1 for details on the procedures to be completed during Screening.

Subjects will also be instructed to apply a bland emollient twice a day to affected areas for the duration of the study (investigators are free to recommend the preferred bland emollient for subject use and the cost will be reimbursed by the Sponsor). To allow for assessment of dryness and scaling, emollients should be avoided during the 4 hours prior to evaluation. All screening laboratory tests must be reviewed by study staff prior to Baseline (D1) to confirm eligibility.

AD severity and impact will be assessed as follows:

By the subject:

- Peak Pruritus Numerical Rating Scale (PP-NRS): a single self-reported item designed to measure peak pruritus or 'worst' itch, over the previous 24 h based on the following question: 'on a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?" (37). See Section 16.1, Appendix A. The PP-NRS (daily itch diary) will be distributed at start of Screening and will be reviewed by study staff at the Baseline Visit (D1). Instruct the subject to complete the daily PP-NRS (daily itch diary) for the 7 days prior to the Baseline Visit to calculate the subjects' baseline average score. Subsequently, the daily PP-NRS will be captured for each day (24 hours previous).
- Dermatology Life Quality Index (DLQI): a 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. See Section 16.2, Appendix B.
- Patient Oriented Eczema Measure (POEM): 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. See Section 16.3, Appendix C.

By the Investigator:

- Investigators Global Assessment (IGA): Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) scale is a 5-point categorical scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on the overall appearance of the lesions at a given time point. Note that to qualify for eligibility, the IGA score must be ≥ 3. See Section 16.4, Appendix D. Note also that IGA-1 should not include scaling or induration. To allow for assessment of dryness and scaling, emollients should be avoided during the 4 hours prior to evaluation.

- Eczema Area and Severity Index (EASI): EASI score measures 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. The total EASI score ranges from 0 (minimum) to 72 (maximum) points; higher scores reflecting the worse severity of AD. Note that to qualify for eligibility, the EASI score must be ≥ 16. See Section 16.5, Appendix E.
- Percent body surface area (BSA) of AD involvement with maximum percentages for each region using the "rule of nines": head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]. The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with AD. The area represented by the palmar surface of the subject's hand with all five digits adducted together, is approximately 1% of the subject's BSA, regardless of the subject's age. Handprints across various body regions assessed is used to calculate BSA % of AD involvement. Note that to qualify for eligibility, the BSA % score for AD involvement must be ≥ 10. See Section 16.6, Appendix F.
- Severity scoring of AD (SCORAD): a 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). Each item is be scored on the most representative area for a given intensity item. See Section 16.7, Appendix G. To allow for assessment of dryness and scaling, emollients should be avoided during the 4 hours prior to evaluation.

7.1.2. D1: Baseline and Study Treatment Administration

7.1.2.1. Prior to Subcutaneous Injection of Study Treatment

Subjects who meet the selection criteria at the Screening Visit and are eligible to participate in the study will be required to return to the study center within 45 days of Screening. The following assessments will be performed (see the Baseline pre-dose procedures as detailed in the Schedule of Events, Table 1):

- Confirm informed consent and eligibility for study participation (note this may require an updated medical history)
- Review the PP-NRS daily diary for completion, confirmation that a bland emollient has been applied to affected areas for at least 7 days before the baseline visit
- Document any new or changed concomitant medications
- Document any AEs
- Document vital signs (VS). Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS
- Obtain ECG and Safety labs (CBC, chemistry, UA), PK, PD and ADA samples, urine pregnancy test

- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (complete patient reported outcomes DLQI and POEM; review PP-NRS diaries with subject)
- Randomize to study treatment regimen
- Instruct subject to continue applying the bland emollient twice daily to affected areas, schedule when to return for the next visit. Remind the subject to complete the daily PP-NRS (daily itch diary) and perform required study procedures

7.1.2.2. Subcutaneous Administration of Study Treatment

Injections will be administered by the Investigator or designee clinical staff. Further details are provided in the CBP-201 Pharmacy Manual. On D1, subjects will receive injections from 4 vials of either CBP-201 or placebo. Study treatment will be administered SC using aseptic technique. SC injections when 4 vials are to be administered will generally be performed at two or more injection sites in the abdomen (avoid the area proximal to the umbilicus), lateral thigh or upper arm (lateral or posterolateral). Injection sites should be rotated for future injections.

Document the time that the study treatment injection is completed (T0). VS (temperature, blood pressure, respiratory rate and heart rate) should be obtained hourly (T1h and T2h) post injection. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.

Prior to discharge from the site, assess injection sites for any reaction. The use of the Injection Site Assessment form (see Section 16.8, Appendix H) may be helpful to the Investigator to standardize injection site responses (note all clinically significant findings should be considered AEs).

Note: upon discharge of the participants after each dose, it is important to instruct subjects on actions to take if any signs and symptoms of delayed severe allergic reactions such as anaphylaxis occur.

Additionally, instruct the subject to continue the twice daily emollient applications on affected areas, when to return for the next visit and to perform required study procedures. The daily itch diary should be completed each day throughout the study. Should an AD flare occur, the subject should notify the site for acceptable topical steroid treatments.

7.1.2.3. AD Flares and Rescue Treatment

AD is a chronic relapsing skin condition that is characterized by periods of disease flare or escalation of symptoms. Many flare definitions rely on a physician's assessment or subject report (38), however a relatively recent review suggests that an escalation of treatment (or rescue) and days of topical corticosteroid (TCS) use were good indicators of flare and flare duration (39). Therefore, when an AD flare occurs, its onset and duration will be documented as an AE by the location(s) of flare involvement. If the Investigator determines that the flare is severe enough to merit "rescue" treatment, document the choice of TCS and

instructions for its use and the duration of such permitted rescue TCS treatment. The subject need not be discontinued in this situation. Permitted TCS medications to treat AD flares may include the following:

- Cream based preparations or lotion in hair bearing areas
- Low to moderate potency TCS (WHO classification VII-IV) equivalent to class VII – IV according to the U.S classification are allowed. The TCS regimen will be adjusted to the flare activity and tolerability by the subject, and stopped when lesions are cleared.
  - Examples:
    - Methylprednisolone acetate 0.1%
    - Mometasone furoate 0.1%
    - Betamethasone valerate cream 0.1%
- If possible, Investigators should attempt to limit the first step of rescue therapy to permitted TCS rescue treatment and escalate to systemic medications only for patients who do not respond adequately after the treatment of permitted TCS.

If a patient receives any other rescue treatment including other topical rescue treatments (apart from permitted TCS and bland emollients), systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, Janus kinase inhibitors, biologic agents, etc), the study treatment will be immediately discontinued. In this situation, subjects should remain in the study and continue with study procedures (complete the schedule of study visits and assessments) but will not receive additional study drug administration.

Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

7.1.3. D15/W2 Visit

Subjects will return to the study center on W2±2d for study treatment injection and the following assessments (see Schedule of Events, Table 1):

- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment
- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs and obtain PK, PD and ADA samples
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM)
- Perform SC injection

- Record VS pre-dose and q1h x 2 hours (+/- 10 minutes) post dose. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.

On the W2 visit, subjects will receive an injection which may include a vial of both CBP-201 AND placebo or 2 vials of either CBP-201 or placebo. Study treatment will be administered SC using aseptic technique. SC injections when 2 vials are to be administered will generally be performed at one or two injection sites in the abdomen (avoid the area proximal to the umbilicus), lateral thigh or upper arm (lateral or posterolateral). Injection sites should be rotated for future injections.

Prior to discharge from the site, assess injection sites for any reaction. The use of the Injection Site Assessment form (see Section 16.8, Appendix H) may be helpful to the Investigator to standardize injection site responses (note all clinically significant findings should be considered AEs).

Note: upon discharge of the participants after each dose, it is important to instruct subjects on actions to take if any signs and symptoms of delayed severe allergic reactions such as anaphylaxis occur.

Additionally, instruct the subject to continue the twice daily emollient applications on affected areas, when to return for the next visit and to perform required study procedures. Remind the subject that the daily itch diary should be completed each day throughout the study. Should an AD flare occur, the subject should notify the site for evaluation and acceptable TCS treatments.

7.1.4. D29/W4 Visit

Subjects will return to the study center on W4±2d for study treatment injection and the following assessments (see Schedule of Events, Table 1):

- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment
- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs, trough PK, PD and ADA samples per Schedule of Events, Table 1
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM) per Schedule of Events, Table 1
- Perform SC injection
- Record VS pre-dose and q1h x 2 (+/- 10 minutes) hours post dose. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.

On the W4 visit, subjects will receive injections which may include a vial of both CBP-201 AND placebo or 2 vials of either CBP-201 or placebo. Study treatment will be administered SC using

aseptic technique. SC injections when 4 vials are to be administered will generally be performed at two or more injection sites in the abdomen (avoid the area proximal to the umbilicus), lateral thigh or upper arm (lateral or posterolateral). Injection sites should be rotated for future injections.

Prior to discharge from the site, assess injection sites for any reaction. The use of the Injection Site Assessment form (see Section 16.8, Appendix H) may be helpful to the Investigator to standardize injection site responses (note all clinically significant findings should be considered AEs).

Note: upon discharge of the participants after each dose, it is important to instruct subjects on actions to take if any signs and symptoms of delayed severe allergic reactions such as anaphylaxis occur.

Additionally, instruct the subject to continue the twice daily emollient applications on affected areas, when to return for the next visit and to perform required study procedures. Remind the subject that the daily itch diary should be completed each day throughout the study. Should an AD flare occur, the subject should notify the site for evaluation and acceptable TCS treatments.

7.1.5. Q2W Visits from D43/W6 through D113/W16

Subjects will return to the study center on W6±2d and every 2 weeks thereafter through W16±2d for study treatment injection and the following assessments (see Schedule of Events, Table 1 for details):

- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment
- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs, trough PK, PD and ADA samples per Schedule of Events, Table 1
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM) per Schedule of Events, Table 1
- Perform SC injection
- Record VS pre-dose and at 30 min (+/- 10 minutes) post dose. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.
- Subjects will undergo 8 weeks of follow visit culminating in a study completion visit on W24 (Table 1).

On the W6 visit and Q2w thereafter through W16, subjects will receive injections which may include a vial of both CBP-201 AND placebo or 2 vials of either CBP-201 or placebo. Study treatment will be administered SC using aseptic technique. SC injections when 2 vials are to be administered will generally be performed at one or two injection sites in the abdomen (avoid the area proximal to the umbilicus), lateral thigh or upper arm (lateral or posterolateral). Injection

sites should be rotated for future injections.

Prior to discharge from the site, assess injection sites for any reaction. The use of the Injection Site Assessment form (see Section 16.8, Appendix H) may be helpful to the Investigator to standardize injection site responses (note all clinically significant findings should be considered AEs).

Note: upon discharge of the participants after each dose, it is important to instruct subjects on actions to take if any signs and symptoms of delayed allergic reactions occur.

Additionally, instruct the subject to continue the twice daily emollient applications on affected areas, when to return for the next visit and to perform required study procedures. Remind the subject that the daily itch diary should be completed each day throughout the study. Should an AD flare occur, the subject should notify the site for evaluation and acceptable TCS treatments.

7.1.6. Follow-Up Visits (W17 through W24)

After W16 of treatment, subjects will no longer receive any SC treatments but will return for an additional 8 weeks for follow-up visits (W17±3d, W18±3d, W20±3d, W22±3d and W24±3d for additional PK/PD/ADA samples) and various additional study procedures (see Schedule of Events, Table 1 or details). Note that W24 is the end of study (EOS) visit as well Follow up visit assessments:

- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment
- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs, PK, PD and ADA samples per Schedule of Events, Table 1
- ECG at W24 (study completion visit) only
- Physical examination at W24 (study completion visit) only
- Record VS. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM) per Schedule of Events, Table 1

Assess prior injection sites for any reaction. The use of the Injection Site Assessment form (see Section 16.8, Appendix H) may be helpful to the Investigator to standardize injection site responses (note all clinically significant findings should be considered AEs).

Additionally, instruct the subject to continue the twice daily emollient applications on affected areas, when to return for the next visit and to perform required study procedures. Remind the subject that the daily itch diary should be completed each day throughout the study. Should an

AD flare occur, the subject should notify the site for evaluation and acceptable TCS treatments.

7.1.7. Early Termination (ET) Visit (+7d)

Subjects who prematurely discontinue from the study will be requested to come in at their convenience for assessments which are normally planned for the end of the study (see Schedule of Events (Table 1) for details of study procedures), if appropriate, and 2 post-treatment follow-up period visits within the 8 weeks following the last dose of study treatment. If subjects are not willing to return for a full complement of early termination assessments, request that they come in to at least assess for any TEAEs.

- Document reason for and date of decision to ET
- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment
- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs, PK, PD and ADA samples per Schedule of Events (Table 1)
- Physical examination per Schedule of Events (Table 1)
- Record VS. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM) per Schedule of Events (Table 1)

For subjects who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases) and report their ongoing status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contacts, and receipt for sending a registered letter). A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after a minimum of 2 documented attempts (phone, text, e-mail, certified letter, etc.).

7.1.8. Unscheduled Visits

Unscheduled visits may be scheduled at any time if warranted due to the subject's complaints or condition per Investigator discretion. Assessments performed at Unscheduled Visits will be at the discretion of the Investigator. See Schedule of Events (Table 1) for details of study procedures. In addition to appropriate treatment for a TEAE, the investigator may consider performing the following:

- Document reason for the unscheduled visit and any treatments rendered
- Document any new AEs
- Document clinically significant AD flares requiring TCS treatment

- Document any new or changed concomitant medications or treatments
- Subject itch diary review
- Perform prior injection site assessment
- Perform safety labs, PK, PD and ADA samples per Schedule of Events (Table 1)
- Record VS. Note that subjects should be seated and rested for at least 3 minutes prior to assessing VS.
- Repeat Investigator AD assessments (IGA, EASI, BSA and SCORAD) and Subject PROs (review PP-NRS with subject, complete DLQI and POEM) per Schedule of Events (Table 1)

7.2. Discussion of Study Design; Randomization and Blinding

This trial is designed to determine the efficacy of study treatment (CBP-201 vs. placebo) injected SC in treating adult moderate to severe AD.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) or other variables are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment as well as to minimize subject and investigator bias. Double-blinded treatments will be used to reduce potential bias of subjects and investigators during data collection and evaluation of clinical endpoints.

Treatment group assignments will be double-blinded during the study. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. In the PK portion of the study all participating subjects whether randomized to active or placebo will have blood drawn at the specified time points and sent to the bioanalytical laboratory for subsequent processing. As no one at the site is unblinded as to which treatment group any subject is assigned, blinding is preserved with PK sampling.

Under normal circumstances, the blind will not be broken until all participants have completed the study. In case of emergency, and only if the information is required by the Investigator to ensure subject's safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor's designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

8. SELECTION OF STUDY POPULATION

8.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1) Be an adult ≥18 and ≤ 75 years of age at the screening visit (Screening) with atopic dermatitis (according to American Academy of Dermatology Consensus Criteria, Eichenfield 2014, [1]),
   a) present for at least 1 year prior to the baseline visit (Baseline) with an inadequate response, in the judgement of the Investigator, to AD treatment with a topical regimen of corticosteroids, phosphodiesterase inhibitors or calcineurin inhibitors, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effect or safety risks);
   b) per Investigator assessment have the following at Screening and Baseline for AD involvement:
      i. Investigator Global Assessment (IGA) score ≥ 3 (according to Validated Investigator Global Assessment for Atopic Dermatitis [vIGA-AD™] scale, on the 0 to 4 vIGA-AD™ scale, in which 3 is moderate and 4 is severe, see Section 16.4 Appendix D)
      ii. Eczema Area and Severity Index (EASI) score ≥ 16 (see Section 16.5 Appendix E), and
      iii. Body Surface Area (BSA) for total AD involvement ≥ 10% (see Section 16.6 Appendix F)
2) Able and willing to apply a stable dose of a bland emollient twice a day to affected areas for at least 7 days before Baseline and to continue for the duration of the study
3) Females of child-bearing potential (FCBP) must abstain from heterosexual activities or agree to use effective contraception. Women who are post-menopausal, as documented by measurement of FSH, or with documented evidence of surgical sterilization prior to Screening. i.e., tubal ligation or hysterectomy are not considered as FCBP. Males who have not undergone a vasectomy must abstain from heterosexual activities or agree to use effective contraception. All participants must be willing to use effective contraception throughout the entire study period if necessary.
   a) Effective contraception options for participating subjects include:
      i. Abstinence from sexual intercourse
      ii. Using a condom, and a diaphragm or cervical cap, as well as use of a spermicidal (where available)
      iii. Oral contraceptives (the “pill”) for at least 1 month prior to Baseline
      iv. Depo-Provera or injectable birth control or implantable contraception (e.g. Implanon)

v. Intrauterine device (IUD)

4) Able to read and understand, and willing to sign the informed consent form (ICF)
5) Willing and able to comply with clinic visits and study-related procedures

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1) Have any of the following laboratory abnormalities at Screening:
   a. Hemoglobin ≤90% of the lower limit of normal range (LLN)
   b. White blood cell (WBC) below the LLN
   c. Neutrophil count below the LLN
   d. Platelet count below the LLN
2) Have undergone treatment with any of the following
   a. Topical agents such as corticosteroids, phosphodiesterase (PDE) inhibitors, Janus kinase (JAK) inhibitors, tacrolimus or pimecrolimus within 1 weeks prior to Baseline. Note that low to medium topical corticosteroids (TCS) are permitted after randomization to treat AD flares (Section 7.1.2.3).
   b. Prior treatment with dupilumab or any antibody against IL-4Rα or IL-13
   c. Systemic treatment for AD or other condition with steroids or other immunosuppressive/immunomodulating substances, e.g., cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate or oral Janus kinase (JAK) inhibitors within 4 weeks prior to Baseline. Use of steroid inhalers and nasal corticosteroids is allowed.
   d. Cell depleting agents, e.g. rituximab, within 6 months of Baseline or treatment with other biologics within within 5 half-lives (if known) or 3 months prior to baseline visit, whichever is longer
   e. Phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), tanning beds, or any other light emitting device (LED), within 4 weeks of Baseline
   f. ≥2 bleach baths within 2 weeks of Baseline
   g. Prescription emollient to treat AD (e.g. Atopiclair®, MimyX®, Epicerum®, etc.) within 2 weeks of Baseline
   h. Any investigational drug within 30 days or within 5 half-lives, whichever is longer, before Baseline.
   i. Live (attenuated) vaccine within 8 weeks of Baseline.
   j. Treatment with systemic traditional Chinese medicine (TCM) or herbal medications within 4 weeks before Baseline visit or treatment with topical TCM or herbal medications within 1 week before Baseline
3) Have any of the following:

a. Infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks before Baseline, or superficial skin infection, such as impetigo, within 2 weeks before Baseline (subject may be rescreened after infection has resolved)
b. A history of parasitic infection (e.g. helminth), within 6 months of Baseline
c. Per investigator judgement, known or suspected history of immunosuppression within 6 months of Baseline, including a history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, human immunodeficiency virus (HIV), listeriosis, pneumocystosis, or tuberculosis, despite infection resolution; or unusually frequent, recurrent or prolonged infections.
d. Any history of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC)
e. A history of malignancy with the following exceptions: completely treated carcinoma in situ of cervix or non-metastatic squamous or basal cell carcinoma of the skin
f. Positive results at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody with positive HCV RNA polymerase chain reaction; positive HIV serology at screening
g. An allergy to L-histidine, trehalose or Tween (polysorbate) 80
h. Plans to undergo a major surgical procedure during the study
i. Alcohol or drug abuse within 2 years before screening
j. Any medical or psychiatric condition, laboratory or ECG parameter which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study or interfere with the interpretation of study results

4) Women must not be pregnant, planning to become pregnant or breast-feed during the study.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw consent and discontinue participation in the study at any time for any reason. A subject's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented. A subject may be discontinued from the study for any of the following reasons:

- At the request of the Sponsor, regulatory agency, or IRB/IEC
- Subject is lost to follow-up
- Subject treatment allocation is unblinded (i.e., individual code break)
- Death of subject
- A subject may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries, procedures or treatments that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of study treatment, or both
- Subject refuses or is unable to adhere to the study protocol
- Major protocol violation
- Pregnancy
- Use of unacceptable concomitant medication(s)
- It is not considered in the best interest of the subject to continue
- Administrative reasons (e.g., termination of enrollment or study)

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. If a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal in as much detail as possible, although the subject is not obligated to provide such a reason.

If a subject is discontinued while at the clinical site, the early termination procedures should be performed prior to discharge from the clinical site. The investigator should ask the subject to participate in follow-up procedures, provided that the subject has not withdrawn consent for such procedures. If the subject refuses to complete early termination/follow-up procedures or continued data collection, this information will be recorded.

8.4. Study Restrictions

In addition to the criteria described in Section 8.1 and Section 8.2, the subject must agree to abide by all study restrictions. Of course, the Investigator is permitted to use clinical discretion for required concomitant medications or treatments to treat an AE.

Abstain from the following during the study:

- illicit drug use or non-medical use of therapeutic drugs not allowed by the protocol
- the following treatments are not permitted and must result in study treatment discontinuation if started after receiving the first dose of study treatment on D1:
  - Dupilumab or any antibody against IL-4Rα or IL-13
  - Topical agents such as phosphodiesterase (PDE) inhibitors, Janus kinase (JAK) inhibitors, tacrolimus or pimecrolimus
  - Systemic treatment with steroids or other immunosuppressive and/or immunomodulating substances, e.g., cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate or oral Janus kinase (JAK) inhibitors
  - Cell depleting agents, e.g. rituximab or other biologic therapeutics
  - TCM or Herbal medications for AD treatment including topical preparations
  - Use of the following is also prohibited during the study participation:

- Allergen immunotherapy
- Live (attenuated vaccine)
- Phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), tanning beds, or any other light emitting device (LED)
- More than 2 bleach baths per week

9. STUDY TREATMENTS

9.1. Study Treatment

9.1.1. Study Treatment Description

CBP-201 is provided as a single-use 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution (Table 3). Placebo is provided as a single-use 2 mL vial containing 1.2 mL solution without CBP-201 and is identical in appearance.

Table 3. Details of Subcutaneous Study Treatments

Drug code	CBP-201	Placebo
Formulation	CBP-201 is formulated as 150 mg/mL in solution containing inactive excipients including NaCl, Trehalose, Tween80, and L-histidine.	Containing the same excipients without CBP-201 drug substance.
Manufacturer	MabPlex International, Ltd.	MabPlex International, Ltd.

All study treatment vials are blinded and will be identified on the label by vial number.

9.1.2. Selection of Doses

The preliminary safety of CBP-201 was established in a prior phase 1 SAD study (CSR CBP-201AU001) in healthy subjects receiving doses from 75 mg to 600 mg and in a MAD study (Protocol# CBP-201AU002) wherein subjects with AD received 4 weekly doses of 75 mg. 150 mg or 300 mg. Based on these studies, the dose regimens shown in Table 2 are likely to be well tolerated.

9.1.3. Study Treatment Storage

Details of storage conditions are provided in the CBP-201 Pharmacy Manual.

9.1.4. Study Treatment Accountability

All study treatment will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations. Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed and the running inventory. The unused quantities will be returned to the Sponsor's drug supply vendor at the end of the trial or destroyed on site according to the site's SOPs. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. The

Investigator or designee must maintain an inventory record of all dispensed rescue medications to subjects. Additional details are provided in the CBP-201 Pharmacy Manual.

Only eligible subjects participating in the study will receive the study treatment. Only authorized research site staff may supply, prepare or administer the study treatments. Once dispensed, study treatment may not be relabeled or reassigned for use by other subjects.

9.1.5. Control of Study Treatment

Mishandling, potential theft, significant loss of clinical supplies, including study treatments at the site or suspected diversion must be reported to the Sponsor or designee within 24 hours of first knowledge of the issue.

9.2. Treatment Compliance

Because all study treatment is being administered by study personnel, no subject use compliance procedures are necessary.

All drug shipment, receipt, storage, use and destruction at investigational sites will be tracked in study-specific drug logs

10. STUDY PROCEDURES AND ENDPOINTS

10.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the Investigator or designated study personnel. The subject must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject's source records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.2. Demographics and Other Baseline Characteristics

10.2.1. Demographics/Baseline Characteristics

The following demographics will be recorded: age, gender, race, and ethnicity. Additionally, height and weight will be obtained at Screening.

10.2.2. Medical and Surgical History

The complete medical and surgical history will include the history of AD specifically and histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. Subject's medical history will be evaluated by an Investigator for clinical significance. Medical history should be re-reviewed and updated at the Baseline Visit, prior to any treatment with investigational drug.

10.2.3. Medication/Treatment History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history and in the database in the Prior and Concomitant Medications section. Similarly, any treatments received will be recorded in the source documentation as medication history.

Any new medications/treatments during the study will be recorded in source documentation and captured in the appropriate case report form.

10.2.4. Height and Body Weight

Height (cm) and body weight (Kg, in indoor clothing without shoes) will be determined at time points according to Schedule of Events (Table 1).

10.2.5. Vital Signs

Vital signs will consist of blood pressure (BP, mmHg), pulse rate (HR, beats per minute), respiratory rate (RR, breaths/min) and body temperature collected while sitting, following a rest period of at least 3 minutes. Vital signs and temperatures will be assessed at various study time points. If in the opinion of the Investigator the perturbation is considered clinically significant, it will be considered an adverse event.

10.2.6. Physical Examination

At Screening, Week 16 and End of Study/Early Termination visits, a complete physical examination (PE) will be performed which includes the following: General appearance, skin, eyes/ears/nose/throat, head and neck, cardiovascular, respiratory, abdomen, extremities, lymph nodes, musculoskeletal and neurologic. A rectal or genital examination is not required unless necessary to assess for AD involvement. Focused PE will be completed at unscheduled visits with attention to areas affected by atopic dermatitis and to assess injection sites, evaluate any AEs or AEs of special interest (AESIs) (Section 11.1.5).

10.3. Atopic Dermatitis Assessments

Details regarding AD assessments by the subject and Investigator are provided in Section 7.1.1.

10.4. Miscellaneous Safety Assessments

10.4.1. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a central laboratory. Blood samples will be collected, processed, and shipped according to instructions from the central laboratory. Additional samples taken may be necessary to repeat testing following abnormal laboratory results or clinical symptoms necessitate testing to ensure safety at the discretion of the Investigator. Required assessments for blood tests are listed in Table 4.

Table 4. Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count Total and differential (absolute) white blood cell count Platelet count	Sodium Potassium Chloride Carbon dioxide Glucose Total protein Albumin Creatinine Blood urea nitrogen (BUN) Total bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Alkaline phosphatase	Urinalysis with microscopic analysis if abnormal

It is the responsibility of the Investigator to review and sign all lab reports expeditiously, and to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting "NCS" (not clinically significant) or "CS" (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., "CS/mild anemia." In general, and as determined by the investigator, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE. The investigator may use the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (published November 27, 2017 and available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) to assist in the determination of severity and clinical significance.

10.4.2. 12-Lead Electrocardiogram (ECG)

A 12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 5 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT and QTcF intervals. The ECGs will be signed and dated by a medically qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are ex/ < 470 msec for female / male subjects, respectively) will be considered an AE.

10.4.3. Pharmacokinetic and Pharmacodynamic Sampling

PK/PD sampling will be performed according to the Schedule of Events (Table 1).

Whole blood for plasma CBP-201 concentrations will be obtained and analyzed. The individual and treatment regimen group steady-state trough PK profile will be calculated for each treatment

schedule. Changes from Baseline will be summarized with descriptive statistics in serum IL-4, IL-13, IgE, and TARC and peripheral eosinophil counts.

10.4.4. ADA Sampling

ADA sampling will be performed according to the Schedule of Events (Table 1). The ADA serum sample may be taken from the PD sample. All samples that are positive in the ADA assay will be further tested for the presence of anti-CBP-201 neutralizing antibody (Nab).

10.4.5. Sample Handling:

Handling and labeling requirements after the collection of PK/PD/ADA samples are described in detail in the CBP-201 Lab Manual.

10.5. Study Endpoints

10.5.1. Efficacy Endpoints

10.5.1.1. Primary Efficacy Endpoint

Comparing each CBP-201 regimen to placebo:

- EASI-overall: percentage reduction in EASI from Baseline to W16

10.5.1.2. Secondary Efficacy Endpoints

Comparing each CBP-201 regimen to placebo:

- IGA (0-1): Proportion of subjects with both 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 W16 in weekly average PP-NRS
- Number of AD flares from baseline through Week 16
- Number of days with AD flare through Week 16

10.5.1.3. Other Efficacy Endpoints

Comparing each CBP-201 regimen to placebo from Baseline to W16:

- Change in POEM

- Number of subjects with AD flares (defined as escalation of therapy evidenced by TCS usage) from Baseline to W8 and from W8 to W16
- Proportion of subjects achieving ≥ 2-point improvement in IGA from Baseline to W16
- Change in percentage BSA of AD involvement
- Change in SCORAD
- Proportion of subjects achieving ≥ 3-point reduction in weekly average of PP-NRS
- Proportion of subjects achieving ≥ 4-point reduction in weekly average of PP-NRS
- Change in DLQI

10.5.2. Safety Endpoints

Safety will be assessed on basis of:

- AEs reported
- VS, physical examinations and injection site changes
- Safety laboratory parameters and ECG parameters
- Number (%) of subjects displaying positive anti-drug antibodies (ADA)

11. ADVERSE EVENT REPORTING

11.1. Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A "suspected adverse reaction" means any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

11.1.1. AE Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. The relationship of each AE to study medication will be assessed using the following categories:

Causality Category	Description
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator cannot determine the etiology of the event but

determines that investigational product did not cause the event, this should be clearly documented on the case report form and SAE Report Form if applicable.

11.1.2. AE Severity

The investigator may use the CTCAE Version 5.0 to assist in the determination of severity and clinical significance. The following represents CTCAE grading of AE severity:

- **Grade 1 / Mild**: asymptomatic or mild symptoms or clinical or diagnostic observations only or intervention not indicated.
- **Grade 2 / Moderate**: minimal, local or noninvasive intervention indicated or limiting age-appropriate instrumental activities of daily living (ADLs). Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.
- **Grade 3 / Severe or Medically Significant But Not Immediately Life-threatening**: hospitalization or prolongation of hospitalization indicated or disabling or limiting self-care ADLs. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- **Grade 4 / Life Threatening Consequences**: urgent intervention indicated.
- **Grade 5 / Death Related to AE**.

AEs not listed by the CTCAE will be graded as follows:

- **Grade 1 / Mild**: discomfort noticed but no disruption of normal daily activity.
- **Grade 2 / Moderate**: discomfort sufficient to reduce or affect daily activity.
- **Grade 3 / Severe**: inability to work or perform normal daily activity.
- **Grade 4 / Life Threatening**: represents an immediate threat to life.
- **Grade 5 / Death**

11.1.3. Serious Adverse Event (SAE)

An SAE or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in an offspring)

- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance. Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of a persistent pretreatment laboratory abnormality)
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Elective hospitalization, e.g., preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject

11.1.4. General Guidelines for AE Reporting

Collection of AEs and SAEs will commence from the time the subject signs the informed consent to participate in the study and continue until the end of the study. All AEs must be entered on the corresponding pages of the CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant.

Information collected concerning AEs will include the following:

- Name of the event (whenever possible, diagnosis or single syndrome should be reported instead of symptoms)
- Start date
- Stop date
- Severity (i.e., mild, moderate, severe, potentially life-threatening, death)

- Relationship to study treatment (related, not related)
- Action taken with the study treatment (dose not changed, drug interrupted, drug withdrawn, not applicable, unknown)
- Outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, resolved with sequelae, fatal, unknown)
- Seriousness of event (SAE or non-SAE)

Pretreatment AEs are defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation. Treatment-emergent adverse events (TEAEs) are defined as AEs that developed or worsened during the treatment-emergent period. The treatment-emergent period is from first administration of study treatment to end of the follow-up period. Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should not be recorded as AEs unless they worsen in severity or increase in frequency. Screening evaluation findings (e.g., laboratory tests, ECG, etc.) should not be recorded as Pretreatment AEs unless related to study procedures.

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the subjects. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the sponsor. Subjects who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

When treatment is prematurely discontinued, the subject's observations will continue until the end of the study as defined by the protocol for that subject.

Laboratory, vital signs or ECG abnormalities should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

11.1.5. AE of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the

sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

Ophthalmic complications are well known to complicated severe AD with incidence rates of 32-56% (2, 3, 6). Nonetheless, conjunctivitis and keratitis have been subjects of interest in the dupilumab experience. In Akinlade, the authors reported that in the combined dupilumab AD experience (n=1047) there were a total of 90 (8.6%) of patients reporting at least one AE of "conjunctivitis" while those patients in the placebo group (n=517) reported 11 (2.1%) such events. Conjunctivitis AEs were mostly mild to moderate in severity with severe events reported in ≤ 0.5% of the dupilumab combined group vs. ≤ 0.3% of the placebo group. Two patients in the dupilumab group permanently discontinued treatment due to a conjunctivitis event. Onset typically occurred during weeks 4-8 and events became less common with long-term treatment. Conjunctivitis was more common in those patients with severe AD at baseline, those with a prior history of conjunctivitis and those with higher baseline levels of TARC and IgE. Pooled dupilumab data suggested that conjunctivitis incidence may decrease with higher trough concentrations of dupilumab.

Due to the dupilumab experience, conjunctivitis, keratitis and other ophthalmic events will be considered AEs of special interest and should be evaluated by an ophthalmologist and appropriate treatment rendered until resolution.

11.1.6. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event, if the SAE is fatal or life-threatening, notification to sponsor/CRO must be made immediately, irrespective of the extent of available event information. The procedure for reporting an SAE is as follows:

- All SAEs must be reported immediately (within 24 hours of discovery) by email to the CRO:

  24/7 Emergency contact: 919-313-1412 (US toll-free: 1-866-761-1274)

  SAE Reporting email: safety-inbox.biotech@iqvia.com
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will report SAE(s) by completing a SAE Report Form, which is provided by sponsor/CRO. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and

illnesses must be provided. SAE Report Form will include the following information, as available:

- Subject ID
- Country where event occurred
- Event Information
- List of relevant test results and laboratory data
- Any other relevant history
- Whether the study treatment was discontinued
- Investigator's assessment of causality

The CRO Medical Monitor or CRO designee / Sponsor designee may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report form and the AE CRF. The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB/IEC of the occurrence of and details surrounding the event in accordance with local regulations. In the event there is a question as to whether the AE is serious, the event should be reported.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by him/her to be caused by the study medication with a reasonable possibility, should be reported to the monitoring team or sponsor/designee within 24 hours.

11.2. Mandatory Early Termination

Using CTCAE Version 5.0, subjects who develop any possibly related grade 2 or higher cardiovascular or respiratory TEAE or any possibly related grade 3 or higher TEAE involving other organ systems must be discontinued from further study treatment dosing and monitored until resolution or stabilization.

11.3. Pregnancy

All subjects who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation as detailed in the inclusion and exclusion criteria. Pregnancy testing will be conducted throughout the study, as detailed in the Schedule of Events (Table 1).

A subject who is found to be pregnant at the screening visit or during the screening period will be excluded from the study and will be considered to be a screening failure. If any subject who has been enrolled in the study is found to be pregnant during the study, the investigator must notify the CRO and sponsor/designee within 24 hours of learning about the pregnancy, the subject should be withdrawn from the study and any study treatment should be immediately

discontinued. Pregnancy during the study must be reported to CRO and sponsor/designee by completing a Pregnancy Form irrespective of whether an adverse event has occurred. Information submitted should include the anticipated date of delivery. In the case of any pregnancy in the partner of a male subject, the investigator must obtain permission from the subject's partner in order to collect any pregnancy information.

The Investigator will be required to follow the pregnancy up to final outcome (completion or pregnancy termination, including perinatal or neonatal outcome up to 28 days after birth). The outcome including any premature termination must be notified to CRO and reported to sponsor/designee using the Pregnancy Form. An evaluation after the birth of the child will also be conducted.

Although pregnancy occurring in a clinical study is not considered to be an SAE, if the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion includes miscarriage and missed abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

12. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 12.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. The Sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigational site termination and regulatory authority notification.

12.1. Data Collection

Source documents include, but are not limited to, original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor's monitor or designated representative. The Sponsor's monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

12.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor's designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or

endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study treatment stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

13. STATISTICAL METHODS

13.1. Statistical and Analytical Plans

This section describes the statistical methods to be used to analyze the efficacy and safety. The final analysis will be documented in a formal Statistical Analysis Plan (SAP) that will be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

13.2. Sample Size Justification

The first primary efficacy endpoint is percentage of reduction of EASI at week 16. While the final analysis is planned to be analysis of variance (SAS® PROC MIXED for ANOVA) with confounding covariates, for simplicity, the sample size is calculated using a simpler 2-sample independent t-test. Based on the preliminary results at week 4 and more empirical data, the following input parameters were used for power and sample size calculation:

Parameters:

- Type I error (α) = 0.05 (two-sided)
- The non-inferiority margin of 35% between the CBP-201 300 mg Q2W vs. Placebo
- Common standard deviation (σ) = 45%
- Effective sample size: 44 per arm, after considering of 20% dropout rate from 55 randomized per arm

Hypotheses:

H0: $\Delta_{\text{CBP-201-300 mg Q2W - Placebo}} = 0$

H1: $\Delta_{\text{CBP-201-300 mg Q2W - Placebo}} \neq 0$

Statistical test: Two-sample t-test for mean difference

Based on method described above, a sample size of 220 (55 per arm, or effective sample size of 44 per arm considering 20% dropout rate) will provide 95% power to detect the treatment effect on the primary endpoint between the CBP-201 300 mg Q2W vs. Placebo.

To further detect the other treatment effects vs. Placebo, and also preserve the alpha at 0.05 level, a hierarchical multiple testing procedure is adopted, from the highest dose (300 mg Q2W) to the lowest dose (150 mg dose Q2W), until statistical significance at 0.05 level is not achieved.

13.3. Analysis Populations

The following three analysis populations are planned for this study:

- All Subjects Screened (Screened) set will contain all subjects who signed informed consent.
- All Randomized Set (Randomized) will contain all subjects who are randomized into the study, no matter whether they were treated or not.
- The Safety Set (SS) will include all randomized subjects who received at least part of an SC dose of study treatment. SS will be based on the actual treatment received.
- The PK Set (PKS) will include all randomized subjects who receive at least 1 dose of active study treatment and have at least 1 PK sample collected and analyzable.
- The Full Analysis Set (FAS) will include all randomized subjects who receive at least part of an SC dose of study treatment. FAS will be based on the planned treatment received (i.e., "as randomized").
- The Per Protocol Set (PPS) will contain a subset of FAS subjects who do not have any major protocol deviations.

All safety assessments and baseline characteristics will be summarized using the SS. PK analyses will be performed using the PKS. PD and efficacy analyses will be performed using the FAS. PK and safety analysis will be based on the actual treatment received. PD and Efficacy analysis will be based on planned treatment received. 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.

13.4. Planned Analyses

Descriptive statistics will be used to summarize the safety, efficacy, PK and PD data. Descriptive statistics will consist of the number of observations, the number of missing observations, mean, standard deviation (SD), standard error, minimum, median, and maximum. Demographic and baseline characteristics will be listed and summarized.

13.5. Study Subjects and Demographics

13.5.1. Disposition and Withdrawals

The numbers of subjects who screen fail (along with the reason), who were randomized, completed the study, and withdrew (ET), along with reasons for ET, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.5.2. Protocol Deviations

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.

13.5.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, weight, and height) will be summarized for each treatment group and for the overall population by descriptive statistics. Medical history and screening clinical laboratory tests will be listed.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO ATC) classes and preferred terms.

13.5.4. Exposure

Since this is a repeat dose study, study treatment administration will be summarized in terms of treatment regimen group (dose delivered over 16 weeks).

13.5.5. General Considerations

All continuous study assessments will be summarized by treatment and time point (as applicable) using the descriptive statistics n, mean, 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 for ratios, will be provided. All statistical tests will be conducted using 2-sided tests with 5% Type 1 error rates unless otherwise stated. The primary efficacy endpoint will be analyzed using the analysis of variance (ANOVA, SAS PROC MIXED procedure) statistical method. Pairwise comparisons for each treatment group vs. placebo will be performed and a serial gatekeeping procedure will be used for multiplicity adjustment. Changes from baseline for continuous outcomes could be presented as their corresponding continuous measures for post-baseline visits, details will be provided in SAP. All study data used on table and figure generation, together with other clinical meaningful data, will be listed by treatment group, subject and time point.

13.6. Analysis of Efficacy Measures

All continuous efficacy endpoints will be summarized using descriptive statistics by treatment group. The categorical efficacy endpoints will be summarized by number and percentage of subjects for each category. Change from baseline in efficacy endpoints will also be analyzed and graphically presented if appropriate.

13.6.1. Analysis for primary efficacy endpoint

The primary efficacy endpoint will be comparing percentage reduction in EASI from baseline to W16 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 the difference between the CBP-201 vs. placebo at W16 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, 300 mg dose Q4W
3. After a 600 mg loading dose, 150 mg dose Q2W

The data will be analyzed using the analysis of variance (SAS PROC MIXED PROCEDURE FOR ANOVA) model, and a 95% confidence interval for the difference in % reduction in EASI from baseline to W16 between each CBP-201 regimen vs. placebo will be provided.

The primary efficacy analysis will be based on FAS and PPS. The statistical conclusion will be based on FAS only. The testing on PPS are for supporting purpose and no multiplicity justification will be further conducted on analyses using PPS.

13.6.2. Analysis for secondary efficacy endpoint

The secondary efficacy endpoints are as follows:

- IGA (0-1): Proportion of subjects with both IGA score 0 to 1 and a reduction of ≥ 2 points at Week 16
- EASI:
  - EASI-50: Proportion of subjects achieving ≥ 50% reduction of EASI score from Baseline at W16
  - EASI-75: Proportion of subjects achieving ≥ 75% reduction of EASI from Baseline at W16
  - EASI-90: Proportion of subjects achieving ≥ 90% reduction of EASI from Baseline to W16
- Change from baseline to Week 16 in weekly average of PP-NRS
- Number of AD flares from Baseline through W16
- Number of days with AD flare from Baseline through W16

For categorical secondary efficacy endpoints, counts, percentage, and confidence interval obtained based on the Clopper-Pearson method will be presented for each CBP-201 regimen and placebo, respectively. For quantitative secondary efficacy endpoints, the method for statistical analysis is similar to those for primary efficacy endpoints.

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 time. Mean change (±SD) from baseline for P-NRS will be plotted by treatment and scheduled time.

For the secondary efficacy endpoints, summary statistics will be provided by treatment group. The clopper-pearson confidence interval will also be provided for endpoints of proportions. No formal statistical comparison will be performed.

In this study, subjects are permitted to take TCS treatment (rescue) for AD flares. It is expected subjects randomized to placebo arm will require TCS medication more often or for longer periods.

All other details for efficacy analyses will be handled as discussed in the Study's SAP.

13.7. Analysis of Safety

Safety analyses will be conducted using data from the Safety Set (as defined in Section 13.3). Safety data will be summarized using frequency tables (counts with percentages) and will be presented by treatment and scheduled time if applicable. AEs will be classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology. Continuous safety data will be summarized using descriptive statistics by treatment and scheduled time. 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.

13.7.1. Clinical Laboratory Evaluations

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

13.7.2. Vital Signs and ECG

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for vital signs and ECG. Detailed description of the analysis will be included in the Study SAP. The incidence of abnormal ECG findings will be summarized.

13.7.3. Physical Examination Findings

Physical and Injection Site examination data will be presented in the listings. Any new findings of Clinically significant abnormalities in physical exam and injection site findings will be recorded as AEs.

13.8. 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.

13.9. Missing data

For analysis of binary efficacy endpoints, subjects who have no data at a specific time point will be considered as non-responders.

For all numerical summary of the primary efficacy endpoint (change in EASI) and the secondary efficacy endpoint analysis items (changes in IGA, P-NRS, POEM, affected BSA, SCORAD, DLQI), the missing individual value at the time points other than W16, the last observation carried forward (LOCF) will be applied. If the individual value is missing at W16, the worst observation carried forward (WOCF) method will be applied.

Methods for calculating some or all missing data regarding time will be explained in the SAP.

14. SITE AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement between the sponsor and the investigational site.

14.1. Regulatory and Ethical Considerations

14.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor's representatives and/or regulatory authority's representatives at any time.

14.1.2. Ethics Approval

The investigational site's IRB/IEC (if the site is required to use a local IRB/IEC) as well as the central IRB/IEC, must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB/IEC prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB/IEC. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB/IEC.

All relevant correspondence from the IRB/IEC will be forwarded by the respective study site to the Sponsor in a timely fashion.

14.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB/IEC-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights. Prospective participants must also be informed of their right

to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study participants.

The Investigator must maintain the original, signed ICF in the participant's source documents. A copy of the signed ICF must be given to the study participant.

14.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB/IEC, and regulatory agencies (such as the United States FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant's initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB/IEC under an appropriate understanding of confidentiality with such board.

All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement for details.

14.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study treatments, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB/IEC promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

14.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 Section 8, as well as any other documentation defined in the protocol or Clinical Study Agreement. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study treatment for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study treatment for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

14.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term "Investigator" used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

14.6. Protocol Amendments

Approval of a protocol amendment by the Investigator's IRB/IEC must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

14.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly

involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

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16. APPENDICES

16.1. APPENDIX A (PEAK PRURITUS NRS):

PEAK PRURITUS NUMERICAL RATING SCALE (PP-NRS)

On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?

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

16.2. APPENDIX B (DLQI):

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Site No: Date:
Subject Initials/#: Score:

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No Not relevant	☐ ☐ ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐

Please check to make sure that you have answered EVERY question.
Thank you.

DLQI - INSTRUCTIONS FOR USE

The DLQI questionnaire is designed for use in adults (≥16 years old). It is self-explanatory and can be simply handed to the subject who is asked to fill it in without the need for detailed explanation. It usually can be completed in one or two minutes.

SCORING The scoring of each question is as follows:

- Very much scored 3
- A lot scored 2
- A little scored 1
- Not at all scored 0
- Not relevant scored 0
- Question 7, 'prevented work or studying' scored 3

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

HOW TO INTERPRET MEANING OF DLQI SCORES

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

16.3. APPENDIX C (POEM):

PATIENT ORIENTED ECZEMA MEASURE (POEM)

Patient-Oriented Eczema Measure

Please circle one response for each of the seven questions below. Young children should complete the questionnaire with the help of their parents. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your/your child's skin been itchy because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
2. **Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
3. **Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
4. **Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
5. **Over the last week, on how many days has your/your child's skin been cracked because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
6. **Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
7. **Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day

Total Score (maximum 28) _____

Responses are scored as follows:

- No days = 0
- 1-2 days = 1
- 3-4 days = 2
- 5-6 days = 3
- Every day = 4

16.4. APPENDIX D (IGA):

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

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

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

Notes:

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

For example:

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

2. Excoriations should not be considered when assessing disease severity.

16.5. APPENDIX E (EASI):

ECZEMA AREA AND SEVERITY INDEX (EASI)

EASI score measures 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.

The total EASI score ranges from 0 (minimum) to 72 (maximum) points; higher scores reflecting the worse severity of AD.

How to Use EASI

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

1. Select a body region

Four body regions are considered separately:

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

2. Assess the extent of eczema in that body region

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

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

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

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

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

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

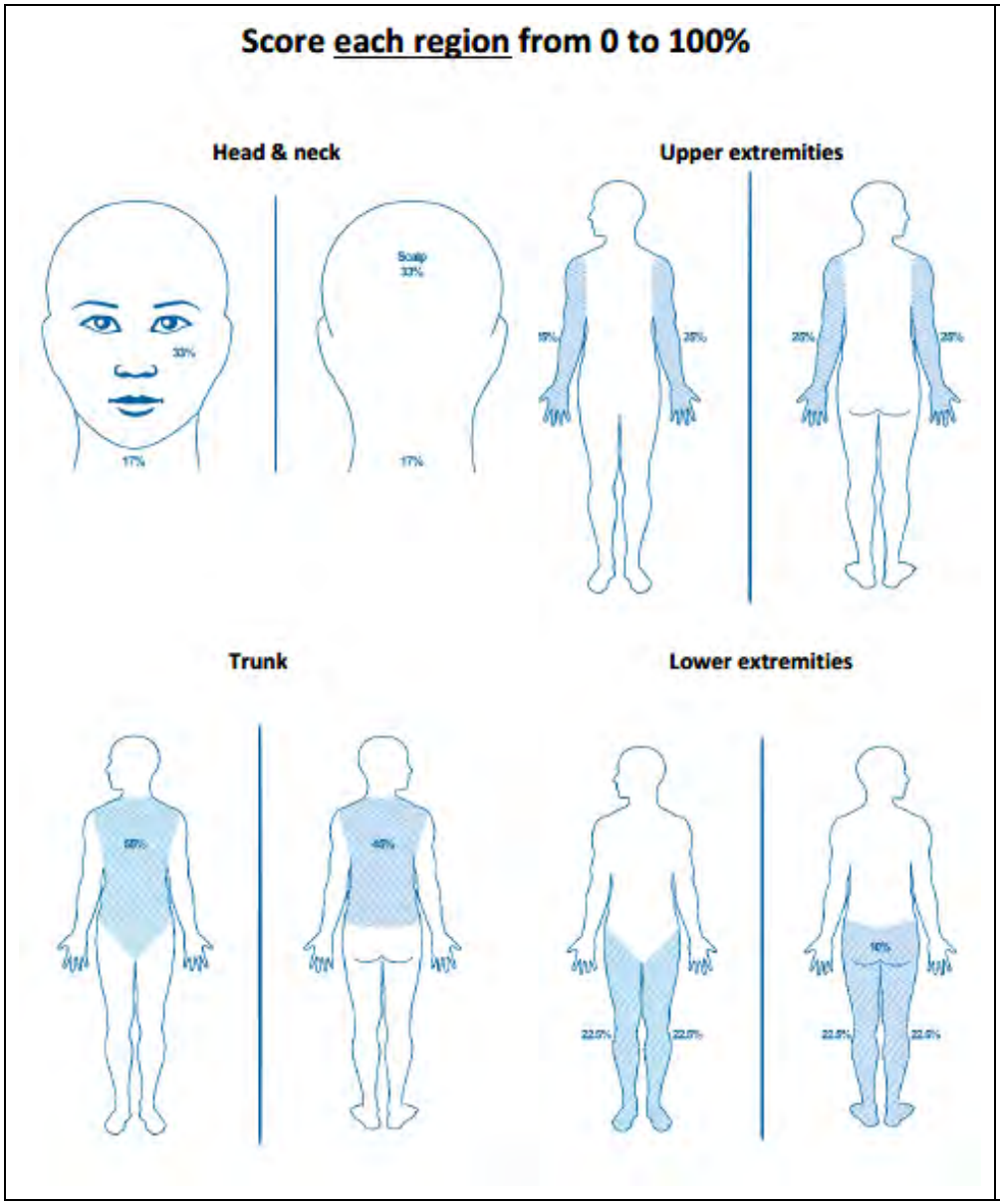
Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

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

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

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


Score each region from 0 to 100%
Head & neck
Upper extremities
Trunk
Lower extremities


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

How to record your scores

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

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

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

What is the difference between edema/papulation and lichenification?
Consider edema/papulation as corresponding to the acute signs of atopic dermatitis that reflect histological spongiosis. Lichenification are more firm thickened plaques with accentuation of the skin markings that develop as a result of prolonged scratching or rubbing in chronic disease. In darker skin types, follicular lichenification may present as firm flat-topped discrete papules. Grade these chronic lesions as lichenification.

How do I grade prurigo nodules?
Prurigo nodules are larger, deeper lesions as a result of chronic scratching and are graded as areas of lichenification.

How do I grade erythema in darker skin?
To avoid underestimating inflammation in patients with darker skin tones, take into account the underlying skin pigment when grading erythema. Often this means increasing your erythema grade by one level.

Can half-steps be used to assess lesion severity?
The original EASI validation study allowed for half steps. These may be helpful when trying to average the severity of a parameter over a region. For example, if there are some areas with an erythema grading of 2 and some areas more consistent with a severity of 3, 2.5 may be a good choice.

What if most areas in a region are a severity grade of 1, but there are some areas that are a grade 3?
Attempt to average the severity across the involved areas in that region. If these areas are close to equal in size, a score of 2 would be most appropriate. If the majority of involved areas are a grade 1, a score of 1 or 1.5 is more appropriate. Be careful not to score the highest severity in a region but the average one.

How do I grade xerosis (dryness), ichthyosis and hyperlinear palms?
Unless there is active acute or chronic eczema overlying these findings, they are not included in the EASI assessment.

How precise should my assessment of eczema extent be?
The *region scores*, which reflect the extent of eczema, were designed and validated as rough estimates of the percentage of involved skin. Each region is given a *score* ranging from 0 to 6, based on a "ballpark" estimation of extent (see region score table in page 1). If you find it difficult to provide a rough estimate of disease extent, you can use the schematics in Appendix 1 to guide you. More time-consuming methods for evaluating disease extent such as the rule of nines or the 'palm' method are generally unnecessary, as the EASI was designed to be…easy.

My patient has responded well to treatment and significantly improved since the last visit. Should I adjust the grading based on the patient's relative improvement?
No. The EASI is a static score, meaning that it is done independently at each time point to reflect current severity. You should grade the EASI per visit regardless of the previous status. Studies have shown that the EASI score has good responsiveness, meaning that overall it is sensitive to change and the improvement will be reflected in the total score.

What do the terms erythema, edema/papulation, excoriation and lichenification mean?
These are key signs of atopic dermatitis. Recognizing and grading them properly requires training on the visual and physical exam consistent with these signs. Generally speaking, erythema is skin redness; edema/papulation refers to an elevation or swelling of the skin (that should be differed from lichenification below); excoriations are scratch marks that have broken the skin surface; and lichenification is a leathery thickening of the skin with exaggerated skin markings.

16.6. APPENDIX F (BSA):

PERCENT BODY SURFACE AREA (BSA) FOR AD INVOLVEMENT

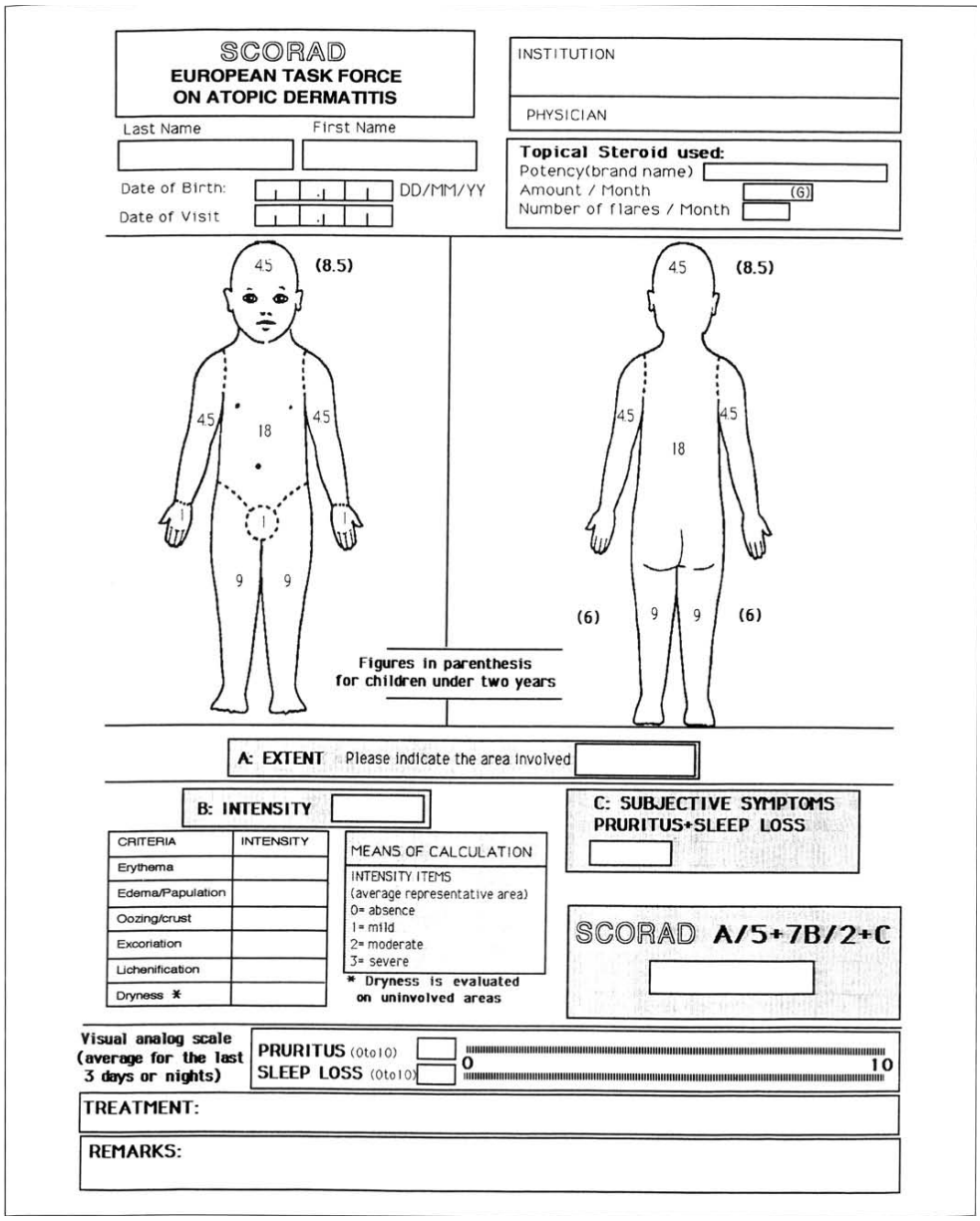
Estimate maximum percentages for each region using the “rule of nines”:

- head and neck [9%]
- anterior trunk [18%]
- back [18%]
- upper limbs [18%]
- lower limbs [36%]
- genitals [1%]

The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with AD. The area represented by the palmar surface of the subject's hand with all five digits adducted together, is approximately 1% of the subject's BSA, regardless of the subject's age. Handprints across various body regions assessed as part of the EASI assessment is used to calculate BSA % AD involvement.

16.7. APPENDIX G (SCORAD):

SEVERITY SCORING OF AD (SCORAD)SCORAD is a 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). Each item is be scored on the most representative area for a given intensity item. Subjective symptoms are graded using a visual analogue scale (VAS) where 0 = no itch (or insomnia) and 10 = worst imaginable itch (or insomnia). The total score is the sum of extent/5 + 7 x intensity/2 + VAS (symptoms) with a SCORAD range between 0 and 103; higher scores reflecting the worse severity of AD.



16.8. APPENDIX H (INJECTION SITE ASSESSMENT):

INJECTION SITE ASSESSMENT

PARAMETER	GRADE	DESCRIPTION
ERYTHEMA	0	NONE
	1	VERY SLIGHT (BARELY PERCEPTIBLE)
	2	SLIGHT (WELL DEFINED)
	3	MODERATE
	4	SEVERE (BEET REDNESS) TO SLIGHT ESCHAR FORMATION (INJURIES IN DEPTH)
DRAINAGE	0	NONE
	1	SEROUS
	2	SEROSANGUINOUS
	3	BLOODY
	4	PURULENT
EDEMA	0	NONE
	1	VERY SLIGHT (BARELY PERCEPTIBLE)
	2	SLIGHT (EDGES WELL DEFINED)
	3	MODERATE (RAISED APPROXIMATELY 1 MM)
	4	SEVERE (RAISED >1 MM AND BEYOND AREA OF EXPOSURE)
INDURATION	0	NONE
	1	MINIMAL
	2	MILD (SPONGY TISSUE)
	3	MODERATE (FIRM, WARM)
	4	SEVERE (HARD, RED, HOT, CREPITUS)
HEMATOMA	0	NONE
	1	MINIMAL
	2	MILD
	3	MODERATE
	4	SEVERE