

# **CLINICAL PROTOCOL**

**NCT04773678**

**Study Number: CBP-201-WW002**

**Title: Multicenter, Randomized, Double-blind, Parallel Group,  
Placebo-controlled, Efficacy and Safety Study of CBP-201 in  
Patients with Moderate to Severe Persistent Asthma with Type 2  
Inflammation**

**V 4.0**

**4 May 2022**

# **CLINICAL STUDY PROTOCOL**

## **A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Efficacy and Safety Study of CBP-201 in Patients with Moderate to Severe Persistent Asthma with Type 2 Inflammation**

**Product:** CBP-201

**Protocol Number:** CBP-201-WW002

**Version Number:** 4.0

**Date of Issue:** 04 May 2022

**Sponsor:** Suzhou Connect Biopharmaceuticals Ltd.

### **Confidentiality Statement**

The information contained in this document is confidential and is provided to you as a potential Investigator or consultant for review by you or your designee(s) and affiliated ethics review committee. Upon acceptance of this document, you agree that the information contained herein will not be disclosed to others without written consent from Suzhou Connect Biopharmaceuticals Ltd, Connect Biopharma Ltd Australia, Connect Biopharma LLC or its affiliates, except to the extent necessary in order to obtain approval of this protocol by an ethical review committee.

Suzhou Connect Biopharmaceuticals, Ltd.  
Investigational Drug: CBP-201

Protocol CBP-201-WW002  
04 May 2022

## SIGNATURE PAGE

**PROTOCOL TITLE:** A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Efficacy and Safety Study of CBP-201 in Patients with Moderate to Severe Persistent Asthma with Type 2 Inflammation

**PROTOCOL NUMBER:** CBP-201-WW002

I agree with the content of this protocol and the confidential nature of the documentation made as part of the study. I also acknowledge that the Investigator has the right to discontinue the study at any time. I have read and understand it and will ensure that the clinical trial is conducted according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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Protocol CBP-201-WW002  
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**PROTOCOL SYNOPSIS**

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Protocol Title:</b>                  | A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Efficacy and Safety Study of CBP-201 in Patients with Moderate to Severe Persistent Asthma with Type 2 Inflammation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Investigational Product:</b>         | CBP-201                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Reference Product:</b>               | Placebo                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Indication:</b>                      | Asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Protocol Number:</b>                 | CBP-201-WW002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Study Phase:</b>                     | Phase 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Investigators and Study Centers:</b> | Approximately 100 sites in the United States, China, the European Union, Ukraine and South Korea                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Number of Patients Planned:</b>      | 306                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Objectives:</b>                      | <p><b>Primary study objective:</b></p> <ul style="list-style-type: none"> <li>To assess the efficacy of CBP-201 versus placebo in patients with moderate to severe persistent asthma with type 2 inflammation as measured by lung function improvements</li> </ul> <p><b>Secondary objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the effect of CBP-201 on the incidence of asthma exacerbations and time to first exacerbation</li> <li>To evaluate the effect of CBP-201 on the weekly average daily lung function relative to placebo</li> <li>To evaluate the safety and tolerability of CBP-201</li> </ul> <p><b>Exploratory objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the effect of CBP-201 on improving patient-reported outcomes, including symptoms, quality of life, and health care resource utilization</li> <li>To characterize the profiles of pharmacodynamic (PD) markers after multiple doses of CBP-201</li> <li>To characterize the pharmacokinetic (PK) profile of multiple doses of CBP-201 in patients.</li> </ul> |
| <b>Study Design:</b>                    | <p>This is a multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess the efficacy and safety of two dose levels of CBP-201 in patients with moderate to severe persistent asthma with Type 2 inflammation.</p> <p>This study consists of 3 periods:</p> <ul style="list-style-type: none"> <li>Screening/Run-in Period (up to 28 days): Determining a patient's eligibility and establishing Baseline before randomization</li> <li>Treatment Period (24 weeks): Patients will be randomized (1:1:1) into 1 of the following dosing groups: CBP-201 150 mg subcutaneous (SC), CBP-201- 300 mg SC, or placebo SC. Each active treatment group will receive a loading dose of 600 mg CBP-201 and the placebo group will receive a volume-matched placebo to maintain the blind.</li> <li>Follow-Up Period (8 weeks): Monitoring a patient's status after they have concluded study drug treatment</li> </ul>                                                                                                                                                  |
| <b>Main Eligibility Criteria:</b>       | <p><b>Inclusion Criteria</b></p> <p>A patient must meet the following criteria to be eligible to participate in this study:</p> <ol style="list-style-type: none"> <li>Adult male or female patient aged 18 to 75 years with a physician diagnosis of asthma for a minimum of 12 months, based on the Global Initiative for Asthma</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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|  | <p>(GINA) 2020 Guidelines.</p> <p>2. Patient is currently receiving treatment with medium to high dose inhaled corticosteroids (ICS) in combination with at least 1 additional reliever/controller for at least 90 days prior to the Screening Visit with a stable dose of ICS at least 28 days prior to the Screening Visit.</p> <p><i>Note:</i></p> <ul style="list-style-type: none"> <li>- Patients receiving ICS equivalent to <math>\geq 226</math> <math>\mu\text{g}</math> fluticasone propionate twice daily or equipotent ICS daily dosage of a maximum of 2000 <math>\mu\text{g}/\text{day}</math> fluticasone propionate (or equivalent) in combination with a second reliever/controller (eg, long-acting <math>\beta</math> agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) are eligible.</li> <li>- Patients receiving fluticasone furoate/vilanterol with fluticasone furoate <math>\geq 200</math> <math>\mu\text{g}</math> once daily are eligible.</li> <li>- Patients receiving budesonide/formoterol with budesonide <math>\geq 640</math> <math>\mu\text{g}/\text{day}</math> are eligible.</li> <li>- Patients requiring a third reliever/controller for their asthma are eligible.</li> <li>- Patients requiring maintenance oral corticosteroids (OCS) with a stable dose <math>\leq 10</math> mg/day prednisone or equivalent OCS in addition to ICS are eligible; OCS total daily dose must have been stable at least 28 days prior to Screening.</li> </ul> <p>3. Prebronchodilator (trough) forced expiratory volume in the first second of expiration (<math>\text{FEV}_1</math>) must be 40 to 85% of predicted normal at Screening <u>and</u> predose Baseline. <i>Note: Patients may repeat pulmonary function testing on a different day if the first attempt fails and justification is documented (e.g., technical issues, reason to suspect longer bronchodilator washout is needed).</i></p> <p>4. Patients must have <math>\geq 12\%</math> reversibility (and <math>\geq 200</math> mL difference) in <math>\text{FEV}_1</math> within 15 to 30 minutes after the administration of up to 4 puffs of albuterol/salbutamol at Screening.</p> <p><i>Note: Patients may repeat reversibility testing on a different day if the first attempt fails and justification is documented (eg, technical issues, reason to suspect that a longer bronchodilator washout is needed).</i></p> <p>5. Blood eosinophil count <math>\geq 300</math> cells/<math>\mu\text{L}</math> at Screening. <i>Note: Patients consented on previous versions of the protocol will not be considered ineligible based on lower eosinophil counts at screening, or at baseline, or in the medical history. Also, patients on maintenance OCS consented on previous versions of the protocol will not be considered ineligible regardless of eosinophil count. Note: If patients' eosinophils are less than 300 cells/<math>\mu\text{L}</math> at Screening, labs may be repeated once within the 28-day Screening Period otherwise they will be screen failed.</i></p> <p>6. Asthma Control Questionnaire (ACQ) score <math>\geq 1.5</math> at Screening and Baseline.</p> <p>7. Patient has experienced an asthma exacerbation at least once in the past 12 months, defined here as:</p> <ul style="list-style-type: none"> <li>- Use of physician prescribed systemic corticosteroid (oral or parenteral), or</li> <li>- Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or</li> <li>- Hospitalization or emergency medical care due to asthma.</li> </ul> <p><i>Note: If patient is maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold is considered adequate to fulfil this criterion. In the event the physician is uncertain that a patient meets the criteria of exacerbation defined within the protocol, the Medical Monitor(s) should be contacted for consultation.</i></p> <p>8. Patient demonstrates acceptable inhaler, peak flow meter, and spirometry techniques during the Screening Period in the opinion of the Investigator.</p> |
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|  | <ol style="list-style-type: none"> <li>9. Patient demonstrates at least 70% compliance with usual asthma controller use during Run-in Period, based on their patient diary in the 7 days prior to dosing.</li> <li>10. Patient demonstrates at least 70% compliance with recording of symptom scores in the patient-reported outcomes (PRO) diary completion during Run-in Period and in their hand-held pulmonary function device in the 7 days prior to dosing.</li> <li>11. Patient is able to understand and willing to sign the informed consent form (ICF).</li> <li>12. Patient is willing and able to comply with clinic visit schedule and study-related procedures, in the opinion of the Investigator.</li> <li>13. Non-sterilized male patients and their female partners of child-bearing potential agree to practice adequate and effective forms of contraception through the duration of the study from first dose to 8 weeks after the last dose of study drug (see Section 4.5.3).</li> <li>14. Female patients of childbearing potential who are sexually active with a non-sterilized male partner agree to practice adequate and effective forms of contraception from first dose to 8 weeks after last dose of study drug (see Section 4.5.3).</li> </ol> <p><b>Exclusion Criteria</b></p> <p>A patient who meets any of the following criteria will be ineligible to participate in this study:</p> <ol style="list-style-type: none"> <li>15. Patient has a current diagnosis of a respiratory disorder other than asthma (eg, active lung infection, chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis) or other disease associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).</li> <li>16. Patient has an acute upper or lower respiratory infection requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent or during the Screening/Run-in Period. <i>Note: Patients must be symptom-free for at least 30 days.</i></li> <li>17. Patient experiences a asthma exacerbation at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit. Exacerbation is defined as: <ul style="list-style-type: none"> <li>- Use of physician prescribed systemic corticosteroid [oral or parenteral], or</li> <li>- Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or</li> <li>- Hospitalization or emergency medical care due to asthma.</li> </ul> <p><i>Note: If patient is maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold is considered adequate to fulfil this criterion. In the event the physician is uncertain that a patient meets the criteria of exacerbation defined within the protocol, the Medical Monitor(s) should be contacted for consultation.</i></p> <p><i>Note: The patient is required to have had at least one exacerbation within the past year but should be stable by the time of the baseline visit. Therefore, the patient should be screened no sooner than 28 days after the last documented exacerbation.</i></p> </li> <li>18. Current smoker or former smoker with a smoking history of &gt; 10 pack-years. <i>Note: This includes tobacco, marijuana, and vaping products.</i></li> <li>19. Patient is undergoing or planning to undergo any elective surgery during the study requiring general anesthesia.</li> </ol> |
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|  | <p>20. Patient has received treatment with any marketed (e.g., omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab) or investigational biologic drug for asthma or other diseases within 16 weeks or 5 half-lives prior to randomization, whichever is longer.</p> <p>21. Patient has received treatment with any investigational nonbiologic drug within 30 days or 5 half-lives prior to randomization, whichever is longer.</p> <p>22. Patient did not respond favorably to previous dupilumab treatment (e.g., therapy failure or patient experienced an adverse reaction to treatment).</p> <p>23. Patient has received specific immunotherapy within 3 months prior to randomization. <i>Note: If the patient has received immunotherapy, a 3-month washout period is required following the last dose of immunotherapy.</i></p> <p>24. Patient is receiving medications or therapy that are prohibited as concomitant medications (See Section 4.5.1).</p> <p>25. Patient has a known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, HIV, listeriosis, pneumocystosis, pulmonary non-tuberculosis mycobacteria, or tuberculosis, regardless of infection resolution; or unusually frequent, recurrent, or prolonged infections. <i>Note: Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees (ECs).</i></p> <p>26. Patient has positive results at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCVAb) with positive HCV RNA polymerase chain reaction; or positive HIV serology at Screening. <i>Note: Patients who test positive for HBcAb, negative for HBsAg and subsequently confirmed positive for HBsAb, indicating resolved natural infection (confirmed by negative HBV-DNA), may participate. Patients with positive HCVAb may participate if subsequent viral load is confirmed negative.</i></p> <p>27. Patient has a helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent that has not been treated with, or has failed to respond to, standard of care therapy.</p> <p>28. Patient shows evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 28 days of Screening, or significant viral infections within 28 days of Screening that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).</p> <p>29. Patient receives live (attenuated) vaccinations within 7 days of Screening or plans to receive live (attenuated) vaccinations during the study.</p> <p>30. Patient has any disorder that is not stable in the opinion of the Investigator and may affect the safety of the patient throughout the study; influence the findings of the studies or their interpretations; or impede the patient's ability to complete the entire duration of study, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment.</p> <p>31. Patient has any clinically significant abnormal findings in physical examination, vital signs, or safety lab tests during Screening/Run-in Period; or any significant medical history which, in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study.</p> <p>32. Patient is being treated with immunosuppressive therapy or biologic therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease,</p> |
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|                                                   | <p>primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis).<br/><i>Note: If patient has previously received therapy for autoimmune disease there should be a washout period of at least 16 weeks.</i></p> <p>33. Patient has a prolonged corrected QT (QTc) interval (male &gt; 450 milliseconds, female &gt; 470 milliseconds) or tachyarrhythmia.</p> <p>34. Patient has any of the following laboratory abnormalities at Screening:</p> <ul style="list-style-type: none"> <li>- Eosinophils &gt; 1500 cells/mm<sup>3</sup> or 1.5*10<sup>9</sup>/L</li> <li>- Platelets &lt; 100000 cells/mm<sup>3</sup> or 100*10<sup>9</sup>/L</li> <li>- Creatine phosphokinase (CPK) &gt; 10 times the upper limit of normal (ULN)</li> <li>- Alanine aminotransferase (ALT) &gt; 2.5 times the ULN</li> <li>- Aspartate aminotransferase (AST) ≥ 2.5 times the ULN</li> <li>- Bilirubin ≥ 2 times the ULN.</li> </ul> <p>35. Patient has a history of alcohol or drug abuse within 12 months of Screening.</p> <p>36. Patient has an allergy to L-histidine, trehalose, or Tween (polysorbate) 80 or a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.</p> <p>37. Patient has a history of malignancy within 5 years prior to the Baseline Visit, with the following exceptions: patients with a history of completely treated carcinoma in situ of cervix and nonmetastatic squamous or basal cell carcinoma of the skin are allowed.</p> <p>38. Female patient is pregnant, planning to become pregnant, or is breastfeeding.</p> |
| <b>Study Duration:</b>                            | Approximately 36 weeks, including a Screening Period of up to 28 days, a 24-week Treatment Period, and an 8-week Posttreatment/Follow-up Period.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Test Products and Route of Administration:</b> | <p>CBP-201 is provided as a 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution at a concentration of 150 mg/mL.</p> <p>Placebo is provided as a 2 mL vial containing 1.2 mL solution containing identical excipients without CBP-201.</p> <p>Study drug will be administered by SC injection by the study team at the site, or by their designee for any home study visits.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Product Dosing:</b>                            | <p>Randomized 1:1:1 to the following treatments:</p> <ul style="list-style-type: none"> <li>• CBP-201 150 mg SC Q2W with a 600-mg loading dose on Day 1</li> <li>• CBP-201 300 mg SC Q2W with a 600-mg loading dose on Day 1</li> <li>• Placebo volume-matched SC dosing Q2W with a placebo loading dose on Day 1</li> </ul> <p>Dosing will be volume matched to maintain double-blind with 4 times 1-mL injections on Day 1 and 2 times 1 mL injections on subsequent dosing days.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Study Endpoints:</b>                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Efficacy:</b>                                  | <p><b>Primary Efficacy Endpoint:</b></p> <ul style="list-style-type: none"> <li>• Absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Week 12</li> </ul> <p><b>Secondary Efficacy Endpoints:</b></p> <ul style="list-style-type: none"> <li>• Absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, 8, and 24</li> <li>• Percent change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, 8, 12, and 24</li> <li>• Change from Baseline in other lung function measurements [percentage predicted FEV<sub>1</sub>, morning and evening peak expiratory flow (PEF) and FEV<sub>1</sub>]</li> <li>• Time to exacerbation and number of events during the 24-week Treatment</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|                                    | <p>Period</p> <ul style="list-style-type: none"> <li>Proportion of patients with <math>\geq 1</math> asthma exacerbation during the 24-week Treatment Period</li> </ul> <p><b>Exploratory Efficacy Endpoints:</b></p> <ul style="list-style-type: none"> <li>Asthma exacerbation rate</li> <li>Change from Baseline at Weeks 1, 2, 4, 12, and 24 in the following symptoms as captured in ePRO: <ul style="list-style-type: none"> <li>Weekly mean asthma symptom score (night-time)</li> <li>Weekly mean rescue medication use</li> <li>Number of nights with awakening due to asthma</li> <li>Weekly mean number of night-time awakenings due to asthma</li> <li>Six-question Asthma Control Questionnaire (ACQ) score</li> <li>Health care utilization</li> </ul> </li> </ul> <p><b>Exploratory Pharmacodynamic Endpoints:</b></p> <ul style="list-style-type: none"> <li>Change from Baseline in FeNO (ppb)</li> <li>Change from Baseline in blood levels of IgE</li> <li>Change from Baseline in blood levels of thymus and activation-regulated chemokine (TARC)</li> <li>Change from Baseline in peripheral eosinophil counts</li> <li>Change from Baseline in other markers of atopic inflammation in the blood (periostin, ECP, CRP, eotaxin-3)</li> </ul> |
| <b>Safety:</b>                     | <p><b>Safety Endpoints:</b></p> <p>Safety endpoints will be summarized by descriptive statistics and narratives where indicated by severity.</p> <ul style="list-style-type: none"> <li>Adverse events reported, including SAEs and AESIs</li> <li>Vital signs measured</li> <li>Electrocardiogram changes</li> <li>Injection site evaluations</li> <li>Safety laboratory parameters evaluated</li> <li>Antidrug antibodies</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Pharmacokinetics (PK):</b>      | <p><b>Pharmacokinetic Endpoints:</b></p> <p>Whole blood for plasma CBP-201 concentrations will be obtained and analyzed. The individual and treatment group steady-state trough PK profile will be calculated.</p> <p>Additional sampling will be obtained after the last treatment dose, as noted in the schedule of assessments, to characterize the return to Baseline.</p> <p>The details of PK analysis will be reported in a separate PK analysis report.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Statistical Considerations:</b> | <p>Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate statistical analysis plan (SAP).</p> <p><b>Analysis Populations:</b></p> <p>Five populations will be defined: Randomized Set, Full Analysis Set, Per Protocol (PP) Set, Safety Analysis Set, and PK Set.</p> <p><b>Randomized Set</b></p> <p>The Randomized Set consists of all patients who are randomized to treatment.</p> <p><b>Full Analysis Set (FAS)</b></p> <p>The primary analyses of all efficacy endpoints will be conducted in the Full Analysis Set (FAS), defined as all randomized patients who receive at least 1 dose</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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|  | <p>of study treatment. The efficacy analyses will be conducted according to the treatment to which the patients are randomized.</p> <p><b>Per Protocol (PP) Set</b></p> <p>The PP Set, a subgroup of the FAS, includes patients without major protocol deviations. Supportive efficacy analyses will be conducted in the PP Set.</p> <p><b>Safety Analysis Set</b></p> <p>The analysis population for the safety endpoints will be the Safety Analysis Set. The Safety Analysis Set consists of all randomly assigned patients who took at least 1 dose of study drug. These patients will be categorized according to the treatment they actually received.</p> <p><b>Pharmacokinetic (PK) Set</b></p> <p>The PK Set consists of all randomly assigned patients from whom at least 1 post-dose PK blood sample was collected.</p> <p><b>Statistical Analysis:</b></p> <p>The primary analysis will be performed in absolute change from baseline to Week 12 in FEV<sub>1</sub> by applying analysis of covariance (ANCOVA) with treatment group, FEV<sub>1</sub> at Baseline and stratification factors as fixed effects. The least squares mean (LSM) and the corresponding 95% confidence interval (CI) will be calculated from the ANCOVA model for each treatment group.</p> <p>Secondary endpoint analyses will be detailed in the SAP. MMRM analyses will be applied to FEV<sub>1</sub> for the time points such as Week 1, 2, 4, 8 and 24 other than Week 12.</p> <p>The MMRM analyses will also be conducted for percent change from baseline to each time point, Weeks 1, 2, 4, 8, 12 and 24 in FEV<sub>1</sub>.</p> <p>Adverse events will be coded using the MedDRA. Treatment-emergent adverse events (TEAEs) are defined as any AEs occurred or worsened during the treatment period, whether considered related to the treatment. The incidence of TEAEs will be presented overall, by system organ class (SOC), and by preferred term for each treatment group. Incidence of AEs by severity and relationship to study drug will also be presented for each treatment group. Deaths, SAEs, injection site reaction, AESIs and adverse events resulting in discontinuation from the study will be summarized by treatment group.</p> <p><b>Sample Size Estimation:</b></p> <p>The sample size of the study is determined based on power calculations for the primary endpoint in patients receiving CBP-201 300 mg Q2W versus placebo. Assuming a common standard deviation of 0.35 L, with 258 randomized patients (randomization ratio of 1:1:1; 86 patients in each group), the study will have 80% power to detect a 0.15 L difference in terms of absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> between CBP-201 300 mg Q2W group versus placebo group at Week 12 at the 2-tailed significance level of <math>\alpha = 0.05</math>. To accommodate a potential dropout rate of 15% the planned total sample size is 306 patients (102/arm).</p> <p>Approximately 60% of the randomized patients will be targeted to have a blood eosinophil count <math>\geq 300</math> cells/<math>\mu</math>L at screening.</p> <p>Randomization will be stratified by central lab blood eosinophil count at Screening (<math>&lt;</math> or <math>\geq 300</math> cells/<math>\mu</math> L). As of Protocol Version 4.0, only patients with at least 300 blood eosinophils/<math>\mu</math>L at screening will be accepted into the study to ensure overall enrichment target of 60%.</p> |
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**Table 1: Schedule of Assessments**

| Assessments                                                | Screening | Baseline | Treatment Period   |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       | Follow-up Period         |    | Unscheduled Visits <sup>s</sup> | Early Termination (+7d) |
|------------------------------------------------------------|-----------|----------|--------------------|---------------------|---------------------|---------------------|---------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------------------|-----------------------|--------------------------|----|---------------------------------|-------------------------|
|                                                            |           |          | D8/<br>W1<br>(±3d) | D15/<br>W2<br>(±3d) | D29/<br>W4<br>(±3d) | D43/<br>W6<br>(±3d) | D57/<br>W8<br>(±3d) | D71/<br>W10<br>(±3d) | D85/<br>W12<br>(±3d) | D99/<br>W14<br>(±3d) | D113/<br>W16<br>(±3d) | D127/<br>W18<br>(±3d) | D141/<br>W20<br>(±3d) | D155/<br>W22<br>(±3d) | EOT<br>D169/W24<br>(±3d) | D197/<br>W28<br>(±5d) | EOS<br>D225/W32<br>(±5d) |    |                                 |                         |
| Visit                                                      | V1        | V2       | V3                 | V4                  | V5                  | V6                  | V7                  | V8                   | V9                   | V10                  | V11                   | V12                   | V13                   | V14                   | V15                      | V16                   | V17                      | NA | NA                              |                         |
| Informed Consent and assign patient number                 | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Demographics and Medical History                           | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Eligibility Criteria                                       | X         | X        |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Height                                                     | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Body Weight                                                | X         | X        |                    |                     |                     |                     |                     |                      | X                    |                      |                       |                       |                       |                       | X                        |                       | X                        |    | X                               |                         |
| FeNO <sup>b</sup>                                          | X         | X        | X                  | X                   | X                   |                     | X                   |                      | X                    |                      | X                     |                       | X                     |                       | X                        | X                     | X                        |    | X                               |                         |
| Spirometry <sup>c</sup>                                    | X         | X        | X                  | X                   | X                   | X                   | X                   | X                    | X                    |                      | X                     |                       | X                     |                       | X                        | X                     | X                        |    | X                               |                         |
| Reversibility <sup>d</sup>                                 | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Complete Physical Examination <sup>e</sup>                 | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       | X                        |    | X                               |                         |
| Brief Physical Examination <sup>f</sup>                    |           | X        | X                  | X                   | X                   | X                   | X                   | X                    | X                    |                      | X                     | X                     | X                     | X                     | X                        | X                     |                          | X  |                                 |                         |
| Vital Signs <sup>g</sup>                                   | X         | 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                        |                       | X                        |    | X                               |                         |
| Hepatitis & HIV Screens <sup>h</sup>                       | X         |          |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |
| Urinalysis <sup>i</sup>                                    | X         | X        |                    |                     | X                   |                     | X                   |                      | X                    |                      | X                     |                       | X                     |                       | X                        | X                     | X                        |    | X                               |                         |
| Pregnancy Test <sup>j</sup>                                | X         | X        |                    |                     | X                   |                     | X                   |                      | X                    |                      | X                     |                       | X                     |                       | X                        | X                     | X                        |    | X                               |                         |
| Dispense or Download Diary and FEV <sub>1</sub> /PEF Meter | X         | X        | X                  | X                   | X                   | X                   | X                   | X                    | X                    | X                    | X                     | X                     | X                     | X                     | X                        | X                     | X                        |    | X                               |                         |
| Review Diary and FEV <sub>1</sub> /PEF Meter Data          |           | X        | X                  | X                   | X                   | X                   | X                   | X                    | X                    | X                    | X                     | X                     | X                     | X                     | X                        | X                     | X                        |    | X                               |                         |
| Randomization                                              |           | X        |                    |                     |                     |                     |                     |                      |                      |                      |                       |                       |                       |                       |                          |                       |                          |    |                                 |                         |

[illegible]

**Abbreviations:** ACQ = Asthma Control Questionnaire; ADA = antidrug antibodies; AE = adverse event; ECG = electrocardiogram; EOS = End-of-Study; EOT = End-of-Treatment;

FE<sub>N</sub>O = fractional exhaled nitric oxide; FEV<sub>1</sub> = forced expiratory volume in the first second of expiration, NAb = neutralizing antibodies; PD = pharmacodynamic(s); PEF = peak expiratory flow; PK = pharmacokinetic(s); SC = subcutaneous; V = visit; VS = vital signs.

### Footnotes:

- a. The screening period to collect baseline data and determine a patient's eligibility is 28 days in duration.
- b. Fractional exhaled nitric oxide (FeNO) assessment is conducted prior to spirometry and following a fast of  $\geq 1$  hour.
- c. Spirometry, including forced expiratory volume in the first second of expiration (FEV<sub>1</sub>), forced vital capacity (FVC), and peak expiratory flow (PEF) will be performed. Due to diurnal variation of lung function it is important that all spirometry assessments after Screening are performed  $\pm 1$  hour in relation to the time of spirometry at Visit 1 and preferably after 7:00 hours and no later than 11:00 hours. Twice-daily long-acting  $\beta$ -agonist (LABA) therapies, including those on combination therapies, should be withheld at least 12 hours; once-daily therapies containing LABA or long-acting muscarinic antagonists (LAMAs) should be withheld for  $\geq 24$  hours prior to all spirometry measurement and reversibility tests. In addition, short-acting  $\beta$ -agonists (SABAs) should not be used within 6 hours prior to the spirometry assessments.
- d. The test is to be performed during the Screening Period. If a patient fails the protocol-specified reversibility or FEV<sub>1</sub> criterion, a second attempt is allowed on a separate day. Retest can be done only once.
- e. A complete physical examination will be performed, which assesses the following: general appearance, head, eyes/ears/nose/throat, neck, thyroid, skin, cardiovascular system, respiratory system, lymph nodes, musculoskeletal system, abdomen, funduscopy (optional), nervous system, and extremities.
- f. A brief physical examination will include an assessment of general appearance, eyes, lungs, and lymph nodes.
- g. Vital signs (VS) include body temperature, respiratory rate, blood pressure, and heart rate. On dosing days, VS should be recorded predose for all visits and hourly ( $\pm 10$  min) during the 2-hour postdose monitoring period on D1 (V2), W2 (V4), and W4 (V5), and at 30 minutes ( $\pm 10$  min) postdose on W6 (V6) and beyond. During the Follow-up Period, VS are to be recorded once during each visit.

Suzhou Connect Biopharmaceuticals, Ltd.  
Investigational Drug: CBP-201

Protocol CBP-201-WW002  
04 May 2022

- h. Hepatitis screen: For more details see Section 7.6.
- i. Urinalysis: pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, leucocytes, and specific gravity.
- j. All women of childbearing potential (WOCBP) will be tested for pregnancy by a serum pregnancy test at Screening and by urine pregnancy tests at Baseline and thereafter. A negative result must be obtained prior to randomization.
- k. Patients are to remain for 2 hours postdose on D1 (V2), W2 (V4), and W4 (V5), and 30 minutes postdose for W6 (V6) and beyond. Assessments and testing should be completed predose except as otherwise noted. Rotate injection sites: abdomen (avoid area proximal to umbilicus), outer thigh, and upper arm (lateral or posterolateral). Only 1 mL should be injected per site, and an injection site should not be repeated more than once per month.
- l. A questionnaire of Health Care Resource Utilization (health care provider visits, hospitalization, emergency or urgent medical care facility visits,) will be administered at Baseline and every 4 weeks through Week 24 and then only Week 32.
- m. Serum chemistry panel: sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), glucose, calcium, uric acid, total protein, total bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), creatine phosphokinase (CPK), total cholesterol, triglycerides, and C-reactive protein (CRP). The blood sample must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours.
- n. Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count with 5-part differential count, differential count, and total red blood cell count.
- o. Pharmacokinetic (PK) blood samples should be collected prior to dosing; date and clock time for each sample should be recorded.
- p. Pharmacodynamic (PD) blood samples for biomarkers of inflammation include eotaxin-3, eosinophil cationic protein (ECP), total immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC) and periostin. Blood eosinophil count will be measured as part of hematology test. CRP will be determined as part of the serum chemistry.
- q. Antidrug antibodies (ADA) blood sample: neutralizing antibodies (NAb) will be examined at all ADA collection time points in samples that are ADA positive. Samples that are ADA negative will not be tested for NAb.
- r. Injection site reactions should be assessed at all visits from the first dosing day until the end of the study. The previous injection site(s) should be assessed prior to dosing and the new injection site should be assessed prior to release. The subcutaneous (SC) injection site may be assessed using a standard instrument provided in Appendix or described as needed by the Investigator in the medical notes. Clinically significant findings as determined by the Investigator will be reported as an adverse event (AE). See section 8.6 for more details.
- s. Unscheduled visits may be conducted as needed, and additional assessments performed at these visits are at the discretion of the Investigator.
- t. Dispense albuterol/salbutamol MDI for reversibility testing and take-home rescue medication. Offer replacements as needed for symptom control throughout the study, reminding to document use in the diary. Prednisone/prednisolone tablets may also be provided, based on Investigator judgement, at the initial visit to be held by the patient in case of exacerbation. The patient is to call the clinic before using this emergency supply of prednisone/prednisolone.

**LIST OF ABBREVIATIONS**

| <b><u>ABBREVIATION</u></b> | <b><u>TERM</u></b>                                         |
|----------------------------|------------------------------------------------------------|
| ACQ                        | Asthma Control Questionnaire                               |
| ADA                        | antidrug antibody                                          |
| AE                         | adverse event                                              |
| AESI                       | adverse event of special interest                          |
| ALP                        | alkaline phosphatase                                       |
| ALT                        | alanine aminotransferase                                   |
| AST                        | aspartate aminotransferase                                 |
| ATS                        | American Thoracic Society                                  |
| BUN                        | blood urea nitrogen                                        |
| CFR                        | Code of Federal Regulations                                |
| COPD                       | chronic obstructive pulmonary disease                      |
| CPK                        | creatine phosphokinase                                     |
| CRO                        | contract research organization                             |
| CRP                        | C-reactive protein                                         |
| CV                         | curriculum vitae                                           |
| EC                         | Ethics Committee                                           |
| ECG                        | Electrocardiogram                                          |
| ECP                        | eosinophil cationic protein                                |
| eCRF                       | electronic case report form                                |
| EMA                        | European Medicines Agency                                  |
| EOS                        | End of Study                                               |
| EOT                        | End of Treatment                                           |
| ERS                        | European Respiratory Society                               |
| EU                         | European Union                                             |
| FAS                        | Full Analysis Set                                          |
| FDA                        | Food and Drug Administration (US)                          |
| FeNO                       | fractional exhaled nitric oxide                            |
| FEV <sub>1</sub>           | forced expiratory volume in the first second of expiration |
| FVC                        | forced vital capacity                                      |
| GCP                        | Good Clinical Practice                                     |
| GGT                        | gamma-glutamyltransferase                                  |
| GINA                       | Global Initiative for Asthma                               |
| HBcAb                      | hepatitis B core antibody                                  |
| HBsAb                      | hepatitis B surface antibody                               |

| <b><u>ABBREVIATION</u></b> | <b><u>TERM</u></b>                                  |
|----------------------------|-----------------------------------------------------|
| HBsAg                      | hepatitis B surface antigen                         |
| HBV                        | hepatitis B virus                                   |
| hCG                        | human chorionic gonadotropin                        |
| HCV                        | hepatitis C virus                                   |
| HCVAb                      | HCV antibody                                        |
| HIPAA                      | Health Insurance Portability and Accountability Act |
| ICH                        | International Conference on Harmonisation           |
| ICF                        | informed consent form                               |
| ICS                        | inhaled corticosteroid(s)                           |
| IFN- $\gamma$              | interferon-gamma                                    |
| IgE                        | immunoglobulin E                                    |
| IL                         | interleukin (IL-4, IL-13, etc)                      |
| IMP                        | Investigational Medicinal Product                   |
| IRB                        | Institutional Review Board                          |
| IUD                        | intrauterine device                                 |
| LABA                       | long-acting $\beta$ adrenergic agonist              |
| LAMA                       | long-acting muscarinic antagonist                   |
| LDH                        | lactate dehydrogenase                               |
| LTRA                       | leukotriene receptor antagonist                     |
| MedDRA <sup>®</sup>        | Medical Dictionary for Regulatory Activities        |
| NAb                        | neutralizing antibody                               |
| OCS                        | oral corticosteroids                                |
| PEF                        | peak expiratory flow                                |
| PK                         | pharmacokinetic(s)                                  |
| PD                         | pharmacodynamic(s)                                  |
| PP                         | Per Protocol (Population)                           |
| ppb                        | parts per billion                                   |
| PRO                        | patient-reported outcomes                           |
| Q2W                        | once every 2 weeks                                  |
| QTc                        | corrected QT (interval)                             |
| SABA                       | short-acting $\beta$ agonist                        |
| SAE                        | serious adverse event                               |
| SAP                        | statistical analysis plan                           |
| SC                         | Subcutaneous                                        |
| SOC                        | system organ class                                  |
| SUSAR                      | suspected unexpected serious adverse reaction       |

| <b><u>ABBREVIATION</u></b> | <b><u>TERM</u></b>                        |
|----------------------------|-------------------------------------------|
| TARC                       | thymus and activation-regulated chemokine |
| T <sub>H</sub> 1           | T helper type 1 cell                      |
| T <sub>H</sub> 2           | T helper type 2 cell                      |
| ULN                        | upper limit(s) of normal                  |
| US                         | United States                             |
| VS                         | vital signs                               |
| WHODrug                    | World Health Organization Drug Dictionary |
| WOCBP                      | women of childbearing potential           |

## 1.0 INTRODUCTION

### 1.1 Background

Asthma affects more than 300 million people worldwide (Olin 2014). Ten to 15% of this population have moderate to severe asthma, which remains refractory to currently available treatments. These patients experience a greater risk of disease exacerbation, hospital admission, and death, as well as a consistently lower quality of life (Bateman 2015; Chung 2014). Patients with severe persistent uncontrolled asthma are those whose symptoms, exacerbations, and limited airflow continue in spite of treatment with medium-to-high-dose inhaled corticosteroids (ICS) and a second added controller drug or systemic corticosteroids (Chung 2014; Global Initiative for Asthma [GINA] 2020). Many patients experience adverse effects of systemic and inhaled corticosteroids on adrenal function, bone metabolism, and growth in children. Phenotyping has recently contributed to the understanding of underlying disease and treatment response to pharmacological agents (Chung 2018; Fitzpatrick 2017).

Asthma is characterized by variable airway symptoms; physiology (airway caliber and hyperresponsiveness); exacerbations of disease; and an infiltration of the bronchial mucosa with activated T cells, eosinophils, and to a lesser extent, polymorphonuclear leukocytes (Davies 1997; Djukanovic 1990). These cells, along with resident airway mast cells, secrete a variety of soluble mediators that directly damage the mucosal surface and perpetuate tissue damage by amplifying the original inflammatory response. As a result, the asthmatic airway undergoes epithelial denudation, subepithelial fibrosis, mucus gland hypertrophy, mucus hypersecretion, and smooth muscle hypertrophy. Through mechanisms that are not yet entirely clear, airway inflammation leads to a persistent augmentation of bronchoconstriction in response to allergens, adenosine monophosphate, and nonspecific stimuli such as inhaled methacholine.

Cells with a T helper type 2 (T<sub>H</sub>2) cell secretion profile are found in the airways of asthmatics. Upon activation, these cells secrete interleukin (IL)-4, IL-5, IL-9, and IL-13 (Umetsu 1997). In contrast, T helper type 1 (T<sub>H</sub>1) cells produce IL-2, IL-12, tumor necrosis factor- $\beta$ , and interferon-gamma (IFN- $\gamma$ ) when stimulated. T cells with a T<sub>H</sub>2 cytokine secretion profile are considered to have a central role in orchestrating the inflammatory response (Robinson 1992; Coyle 1995). Interleukin-4 and IL-13 are believed to be pivotal mediators at all levels of the allergic process in asthma (Coyle 1995; Zhu 1999), as they activate the vascular endothelium, promoting the attachment and infiltration of T cells and eosinophils into lung tissues (Ryan 1997; Savelkoul 1996). Interleukin-4 and IL-13 also promote the synthesis of mediators of the acute allergic reaction, such as immunoglobulin E (IgE) (Chomarat 1997). Additionally, IL-4 stimulates mucus cell metaplasia and the production of mucins (glycoproteins that are the principal constituent of mucus), thus contributing to airflow obstruction (Coyle 1995; Zhu 1999; Ryan 1997; Savelkoul 1996; Chomarat 1997).

Management of severe and treatment-resistant asthma usually includes high-dose ICS and long-acting  $\beta$ -agonist (LABA), as well as a maintenance dose of oral corticosteroids (OCS) (Chung 2018). The European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force on severe asthma recently recommended use of anti-IL-5 and anti-IL-5-receptor alpha (IL-5R $\alpha$ ) for severe uncontrolled adult eosinophilic asthma phenotypes (Holguin 2020). The Task Force also suggests use of anti-IL-4/IL-13 drugs for adult patients with severe corticosteroid-dependent and severe eosinophilic asthma irrespective of blood eosinophil levels (Holguin 2020).

## 1.2 Investigational Product

CBP-201 is a novel human monoclonal antibody directed against the cell surface protein IL-4R $\alpha$ . It is an Investigational Medicinal Product (IMP) currently in development as a treatment for allergic inflammatory diseases by Suzhou Connect Biopharmaceuticals, Ltd (referred to here as CONNECT). In vitro and in vivo nonclinical studies have been conducted to characterize the pharmacologic properties of CBP-201, confirming the mechanism of action and determining potential toxicities of CBP-201 in human patients. Because CBP-201 is a monoclonal antibody that binds to the same immune target as an already marketed antibody against the IL-4R $\alpha$ , Dupixent® (dupilumab) (Dupixent® 2019), the CBP-201 clinical development strategy has been informed by clinical experience of a product in this therapeutic class.

## 1.3 Effects in Humans

CONNECT has completed 3 Phase 1 clinical studies and is in progress with 3 Phase 2 clinical studies and 1 Phase 2/3 clinical study in humans to date that are described in this document. The first study was a single ascending dose Phase 1a study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of CBP-201 in healthy volunteers as the first-in-human study in Australia. A second similar single ascending dose study has been completed in healthy volunteers in China. The third study was a multiple ascending dose Phase 1b study to assess safety, tolerability, PK, and PD of CBP-201 in adult patients with atopic dermatitis. A Phase 2 clinical study in patients with atopic dermatitis in the United States (US), Australia, New Zealand, China, and the EU has recently completed dosing and is in the reporting phase. A Phase 2 study in patients with chronic rhinosinusitis with nasal polyposis is on-going in the US with additional planned sites in China and the EU. A Phase 2/3 study in atopic dermatitis patients is also in progress in China.

To date there has been one un-related death from myocardial infarction and 7 additional unrelated serious adverse events (chest pain, rib fracture secondary to auto accident, cholelithiasis, headache, nausea, vomiting and pneumonia) occurring in the recently completed double-blind Phase 2 trial of CBP-201 in patients with moderate-to-severe atopic dermatitis. Most reported TEAEs to date have been mild to moderate in severity. There have been no clinically relevant trends in clinical safety laboratory data or vital sign data across doses or over time up to 1 to 4 months of treatment.

## 1.4 Compliance

This study will be performed in compliance with the protocol, ICH GCP and applicable regulatory requirements.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Study Objective

To assess the efficacy of CBP-201 versus placebo in patients with moderate to severe persistent asthma with type 2 inflammation as measured by lung function improvements.

### 2.2 Secondary Objectives

- To evaluate the effect of CBP-201 on the incidence of asthma exacerbations and time to first exacerbation

- To evaluate the effect of CBP-201 on the weekly average daily lung function relative to placebo
- To evaluate the safety and tolerability of CBP-201

### **2.3 Exploratory Objectives**

- To evaluate the effect of CBP-201 on improving patient-reported outcomes, including symptoms, health-related quality of life and health care utilization
- To characterize the profiles of pharmacodynamic (PD) markers after multiple doses of CBP-201
- To characterize the pharmacokinetic (PK) profile of multiple doses of CBP-201 in patients

## **3.0 INVESTIGATIONAL STUDY PLAN**

### **3.1 Overall Design**

This is a multi-center, randomized, double-blind, parallel group, placebo-controlled study to assess the efficacy and safety of two dose levels of CBP-201 in patients with moderate to severe persistent asthma with Type 2 inflammation.

This study consists of 3 periods:

- Screening/Run-in Period (up to 28 days): Determining a patient's eligibility and establishing Baseline before randomization
- Treatment Period (24 weeks): Patients will be randomized (1:1:1) into one of the following dosing groups: CBP-201 150 mg subcutaneous (SC), CBP-201 300 mg SC, or placebo SC administered every 2 weeks. Each active treatment group will receive a loading dose of 600 mg CBP-201 and the placebo group will receive a volume-matched placebo to maintain the blind
- Follow-Up Period (8 weeks): Monitoring a patient's status after they have concluded study drug treatment

The primary efficacy endpoint will be prebronchodilator (trough) FEV<sub>1</sub> at Week 12.

Additional secondary and exploratory efficacy, pharmacodynamic, safety and pharmacokinetic endpoints will be assessed throughout the 24-week treatment period and the 8-week follow-up period as detailed below in Sections 3.7-3.10.

### **3.2 Dose Escalation Criteria**

Not applicable for this study.

### **3.3 Discontinuation and Study Stopping Rules**

Dosing for any individual patient will be stopped if the patient experiences a possibly drug-related serious adverse event or a possibly drug-related significant non-serious adverse event, which, in the opinion of the investigator, physician or Sponsor's medical representative, warrants discontinuation of the study for that patient's well-being.

Patients should be encouraged to remain in the study even if they have discontinued treatment.

### 3.4 Rationale for Study Design

CBP-201 simultaneously targets the inflammatory actions of both IL-4 and IL-13 of patients with atopic disease. This study is a standard add-on design for a Phase 2 trial in moderate to severe persistent asthma with type 2 inflammation to assess both efficacy and safety of 2 dose levels of CBP-201. There will be a Screening/Run-in period of 28 days in which the patient's asthma and health status will be assessed prior to dosing. At the Screening and Baseline Visits, the patient will be required to withhold morning medications to allow for trough lung function testing prior to receiving IMP. If the patient fulfils the eligibility criteria, they will be randomized to 1 of 3 treatment groups: CBP-201 150 mg Q2W, CBP-201 300 mg Q2W, or placebo Q2W in a 1:1:1 treatment ratio (each active treatment group will also receive a 600 mg loading dose and the placebo group will receive a volume-matched loading dose). The patient will be allowed to continue regular, protocol-permitted, concomitant medications and will be recording use of rescue medications to allow the clinical site to evaluate them for possible exacerbation of their asthma. The patient's trough lung function will be measured throughout the study with the primary endpoint being the forced expiratory volume in the first second of expiration (FEV<sub>1</sub>) at Week 12 of treatment. Patients will also be closely monitored throughout the study with electronic hand-held flow meters and electronic diaries that will be transmitting data to the clinic in real time. Patients will also be attending the clinic at least every 2 weeks for dosing and will be regularly assessed by the physician at these visits. The patients will be treated with IMP for 24 weeks followed by an 8-week follow-up period during which lung function and other efficacy assessments along with safety will be monitored.

### 3.5 Study Duration

The study duration is approximately 36 weeks including a Screening/Run-in Period of up to 28 days, a 24-week Treatment Period, and an 8-week Follow-up Period.

### 3.6 Study Population

It is anticipated that approximately 306 male and female patients with moderate to severe persistent asthma with Type 2 inflammation will be dosed. Type 2 inflammation is defined in the GINA Guidelines as blood eosinophils  $\geq 150$  cells/uL and/or FENO  $\geq 20$  ppb and/or sputum eosinophils  $\geq 2\%$  and/or asthma that is clinically allergen-driven and/or the patients have a need for maintenance oral corticosteroid therapy. For the purposes of this study, Type 2 inflammation will be defined as at least 150 blood eosinophils/uL at screening or baseline or in the medical history and/or patients on maintenance OCS. The study will be enriched (target of approximately 60%) with patients having at least 300 blood eosinophils/uL at screening or in the medical history for the past 12 months.

### 3.7 Efficacy Assessments

#### 3.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Week 12.

#### 3.7.2 Secondary Efficacy Endpoints

- Absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, 8 and 24
- Percent change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, 8, 12

and 24

- Change from Baseline in other lung function measurements (percentage predicted FEV<sub>1</sub>, morning and evening peak expiratory flow [PEF] and FEV<sub>1</sub>)
- Time to exacerbation events during the 24-week Treatment Period and number of events during the 24-week Treatment Period
- Proportion of patients with  $\geq 1$  asthma exacerbation during the 24-week Treatment Period

### **3.7.3 Exploratory Efficacy Endpoints**

- Asthma exacerbation rate
- Change from Baseline at Weeks 1, 2, 4, 12 and 24 in the following symptoms:
  - Weekly asthma symptom score (night-time)
  - Weekly mean rescue medication use
  - Number of nights with awakening due to asthma
  - Weekly mean number of night-time awakenings due to asthma
  - Six-question Asthma Control Questionnaire (ACQ) score
  - Health care utilization

### **3.8 Exploratory Pharmacodynamic Endpoints**

- Change from Baseline in FeNO (ppb)
- Change from Baseline in blood levels of IgE
- Change from Baseline in blood levels of TARC
- Change from Baseline in peripheral eosinophil counts
- Change from Baseline in other markers of atopic inflammation in the blood (periostin, ECP, eotaxin-3, CRP)

### **3.9 Pharmacokinetic Endpoints**

- Standard population PK endpoints

### **3.10 Safety Endpoints**

Safety endpoints will be summarized by descriptive statistics and narratives where indicated by severity.

- Adverse events (AEs) reported, including serious AEs (SAEs) and AEs of special interest (AESIs)
- Vital signs measured
- Electrocardiogram (ECG) changes
- Injection site evaluations
- Safety laboratory parameters evaluated

- Antidrug antibodies

The immunogenicity of CBP-201 with prolonged use will be determined with the collection of blood samples for measurement of anti-CBP-201 antibodies throughout the study. Further, neutralizing activity will be measured on samples that test positive for anti-CBP-201 antibodies.

## 4.0 STUDY TREATMENTS

### 4.1 Study Drug Description

CBP-201 is provided as a 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution at a concentration of 150 mg/mL. Placebo is provided as a 2 mL vial containing 1.2 mL solution containing identical excipients without CBP-201.

### 4.2 Study Drug Administration

Randomized 1:1:1 to the following treatments:

- CBP-201 150 mg SC Q2W with a 600-mg loading dose on Day 1
- CBP-201 300 mg SC Q2W with a 600-mg loading dose on Day 1
- Placebo volume-matched SC dosing Q2W with a placebo loading dose on Day 1

Dosing will be volume matched to maintain double-blind with 4 times 1-mL injections on Day 1 and 2 times 1 -mL injections on subsequent dosing days.

### 4.3 Rescue Medications

Patients may be provided and/or allowed the following GINA-recommended rescue therapies ([GINA 2020](#)):

- Albuterol (also known as salbutamol, short-acting  $\beta$  agonist [SABA] inhaler). *Note: Patient is allowed to use albuterol/salbutamol as needed and use will be documented daily via diary entry by the patient. An increase of 6 or more reliever occasions (1 puff = reliever occasion) in a 24-hour period for  $\geq 2$  consecutive days along with decreased peak flow will fulfill the definition of “loss of asthma control”.*
- Increase in dosage of inhaled corticosteroids. *Note: An increase of more than 2x the normal dosage of inhaled corticosteroids in a 24-hour period for  $\geq 2$  consecutive days along with decreased peak flow will fulfill the definition of “loss of asthma control”.*
- Oral corticosteroids. *Note: Any **increased** use of oral prednisone/prednisolone or other OCS by the patient will fulfill the definition of “exacerbation” (see Section 5.5.1.1). **Patient should be instructed to contact the clinic before increasing their dose of prednisone/OCS.** Note: A stable dosage of  $\leq 10$  mg/day prednisone or equivalent OCS is allowed under inclusion criterion 2. For those patients on OCS at the start of the study, only a  $\geq 2$ -fold increase in dosage in response to symptoms will fulfill the definition of “exacerbation.”*

If an AE develops requiring the administration of either of these rescue medications, the AE, the rescue therapy administered, and any subsequent action must be recorded in the source documents and electronic case report form (eCRF).

A patient may use a different SABA reliever other than that provided (eg, a different brand of albuterol/salbutamol/levalbuterol that is distributed at screening). All SABA inhaler dosing (puffs) must be recorded in the daily diary. The use of any form of SABA during the study should be factored into the overall use of reliever/rescue medication and in determining whether a patient meets the criteria of exacerbation as defined in the protocol.

***A note about SABA use and recording.*** “Albuterol PRN” may be entered into the concomitant medication CRF but actual use should be captured in responses to daily diary questions about number of puffs used each day/night. Patients should record the use of all SABAs in their daily diary. For example, a patient may receive a ProAir® brand albuterol inhaler at screening but they have a previously prescribed Ventolin® brand albuterol inhaler in their gym bag and a Proventil® brand albuterol inhaler in their desk at work. The number of SABA puffs from all sources, regardless of brand or source (in this example, ProAir plus Ventolin plus Proventil) should be captured in the daily diary with the intention of capturing total SABA usage.

#### **4.4 Other Concomitant Medications**

Patients must be currently receiving daily treatment with medium to high dose ICS in combination with at least 1 additional reliever/controller for at least 90 days prior to the Screening Visit with a stable dose at least 28 days prior to the Screening Visit. The above-mentioned stable dose medication should be maintained during the study as a background therapy for asthma, and dose adjustment is not allowed.

In the interests of the patients’ safety and acceptable standards of medical care, the Investigator will be permitted to prescribe any treatment(s) at his/her discretion. All treatments, including prescription drugs, vitamins, or herbal medications taken within 4 weeks of Screening (Visit 1) and throughout the trial must be recorded in the source documents and eCRF, including indication, dose, unit, route, frequency, and start and stop dates of administration.

#### **4.5 Prohibited Medications and Restrictions**

##### **4.5.1 Prohibited Medications**

Patients may not use any marketed or investigational biologic drug (eg, omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab) within 16 weeks or 5 half-lives prior to randomization and throughout the study.

Patients may not use any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate) within 30 days or 5 half-lives prior to randomization and throughout the study.

Patients may not use any investigational small molecule drug or treatment within 16 weeks or 5 half-lives prior to randomization and throughout the study.

Any increase in the dose of oral corticosteroids (OCS) to help control symptoms during the study will constitute a worsening of asthma, the symptoms of which should be recorded as an AE.

### 4.5.2 Restrictions

Patients should be requested to delay their inhaled medications until after lung function testing as follows:

- Delay SABA for at least 6 hours before Screening (Visit 1)
- Delay the morning dose of inhaled combination therapy or LABA before reversibility, spirometry, and fractional exhaled nitric oxide (FeNO) measurements at Screening (Visit 1)

*Note: On the morning of the Screening Visit, the Patients are requested to delay their morning dose of inhaled bronchodilators (SABA, LABA or other) and combination products, if used regularly, until after pulmonary function testing. If the patient has taken these medications in the morning of the screening visit, patients may continue with screening and return to complete the required pulmonary function tests on another day. Patients may also return for a repeat of reversibility if they fail the initial attempt.*

*Note: If patients forget to delay broncho-dilating medications during the dosing period, lung function measurements should still be completed but flagged in the eCRF with a note to document the last use of the bronchodilator.*

### 4.5.3 Avoidance of Pregnancy

To include women of childbearing potential (WOCBP) in this clinical trial, certain precautions must be taken. These include a serum pregnancy test at Screening (Visit 1), urine pregnancy testing (females of childbearing potential only) throughout the study, as well as requiring the patient to take every precaution to ensure pregnancy does not occur from the first dose to the last visit (8 weeks after the last dose).

In order to prevent pregnancy, all female patients of childbearing potential must use highly effective methods of birth control, defined as those that result in a low failure rate (ie, less than 2% per year) when used consistently and correctly.

Acceptable forms of effective contraception are:

1. Established use of oral, injected, transdermal or implanted hormonal methods of contraception.
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
3. Barrier methods of contraception: Male or female condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should be supplemented with the use of a spermicide. Condoms that are packaged with spermicide fulfil this recommendation. *Note: In countries where spermicide is not available or single barrier methods are not considered highly effective, a second barrier method must be used.*
4. Female sterilization (e.g., documented bilateral tubal ligation, hysterectomy or bilateral oophorectomy).
5. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

6. True abstinence: When this is in line with the preferred and usual lifestyle of the patient (e.g., single sex monogamous relationships, committed absolute abstinence). *Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered true abstinence and are not acceptable methods of contraception.*

In addition, the use of secondary barrier methods (condoms, diaphragms) will be strongly encouraged while participating in this study and for 8 weeks following last dose of study drug.

Female patients not of childbearing potential are those who have undergone bilateral tubal ligation, oophorectomy, hysterectomy, or are postmenopausal and have been amenorrhoeic for greater than 1 year with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms).

As a precaution, all male patients randomly assigned to the study should use an appropriate method of contraception (ie, condom and spermicide) in addition to advising their female partner to use another form of contraception such as those listed above.

If a female patient or a male patient's partner becomes pregnant during the study period (from first dose of study drug until 8 weeks after the last dose), the Investigator will inform the Sponsor and the Institutional Review Board (IRB) or Ethics Committee (EC), as appropriate, as well as providing the appropriate medical follow-up. Patients becoming pregnant while in the study must be immediately withdrawn from treatment and followed to resolution, which includes birth or termination of the pregnancy. Every attempt should be made to follow the pregnancy to completion. If possible, births will be followed by the Investigator for 8 weeks for observation of possible congenital abnormalities. Pregnancies detected prior to randomization at Visit 2 shall be considered screen failure and do not require further follow-up after the patient has been withdrawn from the study.

#### **4.6 Measurement of Patient Compliance**

All dosing is supervised in the clinic or by home healthcare nurses and dosing compliance will be determined from site records and entry into the eCRF. Patient compliance with study procedures at home will be estimated based on review of the patient's daily diary and pulmonary function data at each visit. If the patient is less than 70% compliant with the requirements of the protocol based on review of their diary data, the Investigator or designee must determine if this is a training issue and retrain the patient on use of daily diary and pulmonary function devices. If the patient continues to demonstrate poor compliance (< 70%), their participation should be reviewed with the contract research organization (CRO) and Sponsor to determine if the patient should be withdrawn from the study for failing to comply with the requirements of the protocol.

## 5.0 PATIENT ENROLLMENT

### 5.1 Inclusion Criteria

A patient must meet the following criteria to be eligible to participate in this study:

1. Adult male or female patient aged 18 to 75 years with a physician diagnosis of asthma for a minimum of 12 months, based on GINA 2020 Guidelines.
2. Patient is currently receiving treatment with medium to high dose ICS in combination with at least 1 additional reliever/controller for at least 90 days prior to the Screening Visit with a stable ICS dose at least 28 days prior to the Screening Visit.

*Note:*

- *Patients receiving ICS equivalent to  $\geq 226$   $\mu\text{g}$  fluticasone propionate twice daily or equipotent ICS daily dosage of a maximum of 2000  $\mu\text{g}/\text{day}$  fluticasone propionate (or equivalent) in combination with a second reliever/controller (eg, LABA, leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) are eligible.*
  - *Patients receiving fluticasone furoate/vilanterol with fluticasone furoate  $\geq 200$   $\mu\text{g}$  once daily are eligible.*
  - *Patients receiving budesonide/formoterol with budesonide  $\geq 640$   $\mu\text{g}/\text{day}$  are eligible.*
  - *Patients requiring a third reliever/controller for their asthma are eligible.*
  - *Patients requiring maintenance OCS with a stable dose  $\leq 10$  mg/day prednisone or equivalent OCS in addition to ICS are eligible; OCS total daily dose must have been stable at least 28 days prior to Screening.*
3. Prebronchodilator (trough) FEV<sub>1</sub> must be 40 to 85% of predicted normal at Screening and predose Baseline. *Note: Patients may repeat pulmonary function testing on a different day if the first attempt fails and justification is documented (e.g., technical issues, reason to suspect longer bronchodilator washout is needed).*
  4. Patients must have  $\geq 12\%$  reversibility (and  $\geq 200$  mL difference) in FEV<sub>1</sub> within 15 to 30 minutes after the administration of up to 4 puffs of albuterol/salbutamol at Screening. *Note: Patients may repeat reversibility testing on a different day if the first attempt fails and justification is documented (eg, technical issues, reason to suspect that a longer bronchodilator washout is needed).*
  5. Blood eosinophil count  $\geq 300$  cells/ $\mu\text{L}$  at Screening. *Note: Patients consented on previous versions of the protocol will not be considered ineligible based on lower eosinophil counts at screening, or at baseline, or in the medical history. Also, patients on maintenance OCS consented on previous versions of the protocol will not be considered ineligible regardless of eosinophil count. Note: If patients' eosinophils are less than 300 cells/ $\mu\text{L}$  at Screening, labs may be repeated once within the 28-day Screening Period otherwise they will be screen failed.*
  6. Asthma Control Questionnaire (ACQ) score  $\geq 1.5$  at Screening and Baseline.
  7. Patient has experienced an asthma exacerbation at least once in the past 12 months, defined

here as:

- Use of physician prescribed systemic corticosteroid [oral or parenteral], or
- Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or
- Hospitalization or emergency medical care due to asthma.

*Note: If patient is maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold is considered adequate to fulfil this criterion. In the event the physician is uncertain that a patient meets the criteria of exacerbation defined within the protocol, the Medical Monitor(s) should be contacted for consultation.*

8. Patient demonstrates acceptable inhaler, peak flow meter, and spirometry techniques during Screening Period, in the opinion of the Investigator.
9. Patient demonstrates at least 70% compliance with usual asthma controller use during Run-in Period, based on their patient diary in the 7 days prior to dosing.
10. Patient demonstrates at least 70% compliance with recording of symptom scores in patient-reported outcomes (PRO) diary completion during Run-in Period and in their hand-held pulmonary function device in the 7 days prior to dosing.
11. Patient is able to understand and willing to sign the informed consent form (ICF).
12. Patient is willing and able to comply with clinic visit schedule and study-related procedures, in the opinion of the Investigator.
13. Male patients and their female partners agree to practice adequate and effective forms of contraception through the duration of the study from first dose to 8 weeks beyond the last dose of study drug (see Section 4.5.3).
14. Female patients of childbearing potential who are sexually active with a non-sterilized male partner agree to practice adequate and effective forms of contraception from first dose to 8 weeks after last dose of study drug (see Section 4.5.3).

## **5.2 Exclusion Criteria**

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

15. Patient has a current diagnosis of a respiratory disorder other than asthma (eg, active lung infection, chronic obstructive pulmonary disease [COPD], bronchiectasis, pulmonary fibrosis, cystic fibrosis) or other disease associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
16. Patient has an acute upper or lower respiratory infection requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent or during the Screening/Run-in Period. Note: Patients must be symptom-free for at least 30 days.
17. Patient experiences an asthma exacerbation at any time from 1 month prior to Screening up

to and including the Baseline Visit. Exacerbation is defined as:

- Use of physician prescribed systemic corticosteroid [oral or parenteral], or
- Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or
- Hospitalization or emergency medical care due to asthma.

*Note: If patient is maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold is considered adequate to fulfil this criterion. In the event the physician is uncertain that a patient meets the criteria of exacerbation defined within the protocol, the Medical Monitor(s) should be contacted for consultation.*

*Note: The patient is required to have had at least one exacerbation within the past year **but** should be stable by the time of the baseline visit. Therefore, the patient should be screened no sooner than 28 days after the last documented exacerbation.*

18. Current smoker or former smoker with a smoking history of > 10 pack-years. *Note: This includes tobacco, marijuana, and vaping products.*
19. Patient is undergoing or planning to undergo any elective surgery during the study requiring general anesthesia.
20. Patient has received treatment with any marketed (eg, omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab) or investigational biologic drug for asthma or other diseases within 16 weeks or 5 half-lives prior to randomization, whichever is longer.
21. Patient has received treatment with any investigational nonbiologic drug within 30 days or 5 half-lives prior to randomization, whichever is longer.
22. Patient did not respond favorably to previous dupilumab treatment (e.g., therapy failure or patient experienced an adverse reaction to treatment).
23. Patient has received specific immunotherapy within 3 months prior to randomization. *Note: If the patient has received immunotherapy, a 3 -month washout period is required following the last dose of immunotherapy.*
24. Patient is receiving medications or therapy that are prohibited as concomitant medications (See Section 4.5.1).
25. Patient has a known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, HIV, listeriosis, pneumocystosis, pulmonary non-tuberculosis mycobacteria, or tuberculosis, regardless of infection resolution; or unusually frequent, recurrent, or prolonged infections. *Note: Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or Ethics Committees (ECs).*
26. Patient has positive results at Screening for hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HbcAb), or hepatitis C antibody (HCVAb) with positive HCV RNA polymerase chain reaction; or positive HIV serology at Screening. *Note: Patients who test positive for HbcAb, negative for HbsAg and subsequently confirmed positive for HbsAb,*

*indicating resolved natural infection (confirmed by negative HBV-DNA), may participate. Patients with positive HCVAb may participate if subsequent viral load is confirmed negative.*

27. Patient has a helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent that has not been treated with, or has failed to respond to, standard of care therapy.
28. Patient shows evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 28 days of Screening, or significant viral infections within 28 days of Screening that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).
29. Patient receives live (attenuated) vaccinations within 7 days of Screening or plans to receive live (attenuated) vaccinations during the study.
30. Patient has any disorder that is not stable in the opinion of the Investigator and may affect the safety of the patient throughout the study; influence the findings of the studies or their interpretations; or impede the patient's ability to complete the entire duration of study, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment.
31. Patient has any clinically significant abnormal findings in physical examination, vital signs, or safety lab tests during Screening/Run-in Period; or any significant medical history which, in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study.
32. Patient is being treated with immunosuppressive therapy or biologic therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis). *Note: If patient has previously received therapy for autoimmune disease there should be a washout period of at least 16 weeks.*
33. Patient has a prolonged corrected QT (QTc) interval (male > 450 milliseconds, female > 470 milliseconds) or tachyarrhythmia.
34. Patient has any of the following laboratory abnormalities at Screening:
  - Eosinophils > 1500 cells/mm<sup>3</sup> or  $1.5 \times 10^9/L$
  - Platelets < 100000 cells/mm<sup>3</sup> or  $100 \times 10^9/L$
  - Creatine phosphokinase (CPK) > 10 times the upper limit of normal (ULN)
  - Alanine aminotransferase (ALT) > 2.5 times the ULN
  - Aspartate aminotransferase (AST)  $\geq$  2.5 times the ULN
  - Bilirubin  $\geq$  2 times the ULN.
35. Patient has a history of alcohol or drug abuse within 12 months of Screening.
36. Patient has an allergy to L-histidine, trehalose, or Tween (polysorbate) 80 or a history of a

systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

37. Patient has a history of malignancy within 5 years prior to the Baseline Visit, with the following exceptions: patients with a history of completely treated carcinoma in situ of cervix and nonmetastatic squamous or basal cell carcinoma of the skin are allowed.

38. Female patient is pregnant, planning to become pregnant, or is breastfeeding.

### 5.3 Randomization Procedures

At Screening (Visit 1), potential study patients will be assigned a patient number by site personnel. The patient number is a 6-digit number consisting of a single digit country code, a 2-digit site identifier, and a sequential 3-digit patient number (eg, 3-02-001 for the first screened patient in country 3 at site 02, 3-05-002 for the second screened patient in country 3 at site 05).

All patients entering the double-blind phase of the study will be randomly assigned to receive one of 3 treatments: CBP-201 150 mg SC Q2W, CBP-201 300 mg SC Q2W, or volume-matched Q2W placebo.

Approximately 60% of the randomized patients will be targeted to have a screening blood eosinophil count  $\geq 300$  cells/ $\mu$ L.

Prior to Protocol Version 4.0, randomization was stratified by lab blood eosinophil count at Screening ( $<$  and  $\geq 300$  cells/ $\mu$ L). ***As of Protocol Version 4.0, only patients with eosinophil count  $\geq 300$  cells/ $\mu$ L during the Screening Period will be eligible to participate.*** Note: With implementation of Protocol Version 4.0, patients should be entered into the IRT system exclusively in the  $\geq 300$  eosinophils/ $\mu$ L group. Note: If patients' eosinophils are less than 300 cells/ $\mu$ L at Screening, labs may be repeated once within the 28-day Screening Period otherwise they will be screen failed.

As patients qualify for randomization, they will be assigned to treatment by Interactive Voice/Web Response System. The random treatment assignments will be done in a 1:1:1 ratio.

Given the variable nature of asthma, a screen-failed patient may be re-screened at the Investigator's discretion, at least 28 days after the original Screening Visit date rather than the screen failure date. If re-screened, the patient should be considered under a new patient number.

### 5.4 Blinding Procedures

This is a double-blind study; neither the patients nor the Investigator will be aware of the treatment assignment for the patients. Blinding will be maintained throughout the study by the use of active and placebo treatment vials of similar appearance and volume-matched dosing.

With the exception of the statistician preparing and administering the randomization codes, the staff of Parexel packaging study drug, the staff of Parexel, Syneos, or Frontage involved in processing the PK samples, and quality assurance auditors where necessary, all clinical and nonclinical staff will remain blinded to the treatment allocation until after the study database is locked.

## **5.5 Patient Withdrawal**

### **5.5.1 Reasons for Withdrawal**

All patients have the right to withdraw from treatment or from the study at any time, for any reason, without prejudice. The Investigator may, but is not required to, discontinue any patient's treatment for reasons of non-efficacy of the study drug or other reasons. The Investigator will notify the CRO and Sponsor of all decisions regarding the withdrawal of patients from treatment or from the study.

Patients will be encouraged to remain in the study and on treatment so long as there are no overarching safety concerns about their continued participation.

#### **5.5.1.1 Asthma Exacerbation as Withdrawal Criterion**

If there are safety concerns, the Investigator may, but is not required to, discontinue the patient's treatment for lack of efficacy if the patient experiences an asthma exacerbation as defined as a deterioration of asthma that results in one of the following: hospitalization or urgent medical care due to asthma, treatment with approximately 4 times the patient's normal dose of inhaled corticosteroids, or treatment with systemic steroids. *Note: For patients who are on a maintenance dose of OCS in the study, an exacerbation will be defined as hospitalization or urgent medical care due to asthma, treatment with approximately 4 times the patient's normal dose of inhaled corticosteroids, or 2 or more times increase in their maintenance dose of OCS.*

*Note: Patients may experience symptoms of decreased asthma control that do not reach the level of exacerbation to the point of withdrawal but do warrant concern and attention of the clinic staff. These are termed "loss of asthma control" events and should be considered as an adverse event. (See Section 4.3 for more information).*

The patient should be encouraged to remain in the study and all study procedures should be completed unless the patient withdraws consent or is lost to follow-up.

#### **5.5.1.2 Other Reasons as Withdrawal Criteria**

The Investigator may also discontinue a patient's treatment or study participation for reasons including, but not limited to, the following: AEs deemed by the Investigator to preclude continued study participation, protocol violations, withdrawal of consent, loss to follow-up, death of patient, or termination of the study by the Investigator or Sponsor.

Clinical site staff should confirm loss to follow up with at least 3 documented attempts to contact the patient, at least one of which should be a letter sent by registered mail or other locally customary method.

Patients who develop any possibly related grade 2 or higher cardiovascular, respiratory, or ophthalmic 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.

### **5.5.2 Handling of Withdrawals**

When a patient is withdrawn from treatment or is withdrawn from the study, the reason(s) for withdrawal must be recorded by the Investigator in the patient's medical record and eCRF.

Whenever possible, patients who withdraw from the study prematurely will undergo all end-of-study assessments, ie, Early Termination Visit procedures. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The only exception to this schedule is if patients withdraw prior to randomization at Visit 2. If a patient withdraws or is withdrawn prior to receipt of study drug, this will be considered a screen failure and only the following information need be collected at their last clinic visit: AEs and concomitant medications. The patient will also be required to return to the site and study personnel will collect and review diary and pulmonary function device data.

It is vital to obtain follow-up data or continue visits for any patient withdrawn from treatment because of an AE or SAE. Every effort must be made to undertake protocol -specified safety follow-up procedures. If a patient is discontinued from the study because of an AE, this event will be followed until it is resolved or the patient is clinically stable.

When possible, last observations of clinical data will be carried forward for analysis from all patients who are withdrawn from treatment prematurely.

### **5.5.3 Replacements**

Patients who withdraw or are withdrawn from the trial will not be replaced.

### **5.5.4 Sponsor's Termination of Study**

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

## **6.0 STUDY VISITS**

Patients are requested to delay using bronchodilators prior to each visit (SABA for at least 6 hours, twice-daily LABAs or combination products for at least 12 hours, once-daily bronchodilators or combination products for at least 24 hours).

### **6.1 Screening (Visit 1), Study Day -28 to Day -1**

The following assessments and procedures should be completed in the order given below, if possible.

- Collect signed and dated ICF, Health Insurance Portability and Accountability Act (HIPAA) Form, and Experimental Research Subject's Bill of Rights (if appropriate for that region).
- Receive a 6-digit patient number
- Review inclusion and exclusion criteria
- Complete ACQ
- Record medical history and demographics
- Review and record prior and concomitant medications
- Complete physical examination
- Vital sign measurements
- Record height and weight

- 12-lead ECG
- FeNO assessment to be performed before reversibility and spirometry and following a fast of  $\geq 1$  hour
- Spirometry (Baseline pulmonary function tests)
- Reversibility testing (bronchodilation test)
- Blood collection for pregnancy test for female patients of childbearing potential at Visit 1 then urine pregnancy tests at subsequent visits.
- Safety laboratory samples (hematology, serum chemistry, urinalysis)
- Blood sample for hepatitis and HIV screening
- Dispense and instruct eligible patients on the proper use of the daily electronic handheld device to capture pulmonary function (FEV<sub>1</sub> and PEF) and diary of asthma symptoms
- Dispense take-home rescue medications (albuterol/salbutamol and prednisone/prednisolone) to patients with asthma, if needed. Instruct patients to document the use of albuterol/salbutamol in their diary and to contact the study staff before use of prednisone/prednisolone.
- AE review and recording

Screen failures should be recorded in the eCRF but they do not need to undergo all assessments listed for the Early Termination Visit. The Early Termination Visit assessments should be performed with patients if they withdraw from the study after randomization.

## **6.2 Baseline Visit (Visit 2), Study Day 1**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record prior and concomitant medications
- Record weight
- Brief physical examination
- Vital sign measurements
- 12-lead ECG
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample (pre-dose)
- PD blood sample (pre-dose)
- ADA, NAb blood sample (pre-dose)

- Review daily diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Administer Health Care Resource Utilization questionnaire
- Verify eligibility criteria

If patient does not meet inclusion exclusion criteria based on assessment during Visit 2, the patient will be considered a screen failure.

- Randomization
- Administer study drug
- Injection site assessment
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- AE review and recording

### **6.3 Visit 3 (Study Day 8 ± 3 days/Week 1)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record changes to concomitant medications
- Brief physical examination
- Vital sign measurements
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Hematology and serum chemistry tests
- PK sample
- PD blood sample
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- AE review and recording

### **6.4 Visit 4 (Study Day 15 ± 3 days/Week 2)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and recording of changes to concomitant medications
- Brief physical examination
- Vital sign measurements

- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Review diary and pulmonary function device data
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer study drug
- Injection site assessment
- AE review and recording

### **6.5 Visit 5 (Study Day 29 ± 3 days/Week 4)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record changes in concomitant medications
- Brief physical examination
- Vital sign measurements
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK sample
- PD blood sample
- ADA, NAb blood sample
- Review diary and pulmonary function device data
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer Health Care Resource Utilization questionnaire
- Administer study drug
- Injection site assessment
- AE review and recording

### **6.6 Visit 6 (Study Day 43 ± 3 days/Week 6)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ

- Review and recording of changes in concomitant medications
- Brief physical examination
- Vital sign measurements
- Spirometry (Pulmonary function tests)
- Review diary and pulmonary function device data
- Administer study drug
- Injection site assessment
- AE review and recording

#### **6.7 Visit 7 (Study Day 57 ± 3 days/Week 8)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record changes in concomitant medications
- Brief physical examination
- Vital sign measurements
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- Review diary and pulmonary function device data
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer Health Care Resource Utilization questionnaire
- Administer study drug
- Injection site assessment
- AE review and recording

#### **6.8 Visit 8 (Study Day 71 ± 3 days/Week 10)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record changes to concomitant medications
- Review diary and pulmonary function device data
- Brief physical examination

- Vital sign measurements
- Spirometry (Pulmonary function tests)
- Administer study drug
- Injection site assessment
- AE review and recording

## **6.9 Visit 9 (Study Day 85 ± 3 days/Week 12)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Review and record changes in concomitant medications
- Record weight
- Brief physical examination
- Vital sign measurements
- 12-lead ECG
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- PD blood sample
- ADA, NAb blood sample
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Administer Healthcare Resource Utilization Questionnaire
- Administer study drug
- Injection site assessment
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- AE review and recording

## **6.10 Visit 10 (Study Day 99 ± 3 days/Week 14)**

The following assessments and procedures should be completed in the order given below, if possible:

- Brief physical examination

- Vital sign measurements
- Review and record changes in concomitant medications
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Administer study drug
- Injection site assessment
- AE review and recording

#### **6.11 Visit 11 (Study Day 113 ± 3 days/Week 16)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Brief physical examination
- Vital sign measurements
- Review and record changes in concomitant medications
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer Healthcare Resource Utilization Questionnaire
- Administer study drug
- Injection site assessment
- AE review and recording

#### **6.12 Visit 12 (Study Day 127 ± 3 days/Week 18)**

The following assessments and procedures should be completed in the order given below, if possible:

- Brief physical examination
- Vital sign measurements
- Review and record changes in concomitant medications

- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Administer study drug
- Injection site assessment
- AE review and recording

### **6.13 Visit 13 (Study Day 141 ± 3 days/Week 20)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Brief physical examination
- Vital sign measurements
- Review and record changes in concomitant medications
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer Healthcare Utilization Questionnaire
- Administer study drug
- Injection site assessment
- AE review and recording

### **6.14 Visit 14 (Study Day 155 ± 3 days/Week 22)**

The following assessments and procedures should be completed in the order given below, if possible:

- Brief physical examination
- Vital sign measurements
- Review and record changes in concomitant medications
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Administer study drug
- Injection site assessment

- AE review and recording

### **6.15 Visit 15 (End of Treatment) (Study Day 169 ± 3 days/Week 24)**

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Brief physical examination
- Vital sign measurements
- Record weight
- Review and record changes in concomitant medications
- 12-lead ECG
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- PD blood sample
- ADA, NAb blood sample
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Administer Healthcare Resource Utilization Questionnaire
- Administer study drug
- Injection site assessment
- AE review and recording

### **6.16 Visit 16 (Study Day 197 ± 5 days/Week 28)**

The following assessments and procedures should be completed in the order given below, if possible:

- Brief physical examination
- Vital sign measurements
- Review and record changes in concomitant medications
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)

- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- Review diary and pulmonary function device data; retrain patient on proper diary use, if necessary
- Dispense take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their diary.
- Injection site assessment
- AE review and recording

### **6.17 Visit 17 (End of Study) (Study Day 225 ± 5 days/Week 32)**

The End of Study is defined as the completion of Visit 17 by the last patient.

The following assessments and procedures should be completed in the order given below, if possible:

- Administer ACQ
- Complete physical examination
- Vital sign measurements
- Record weight
- Review and record changes in concomitant medications
- 12-lead ECG
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- PD blood sample
- ADA, NAb blood sample
- Review diary and pulmonary function device data
- Administer Healthcare Resource Utilization Questionnaire
- Injection site assessment
- AE review and recording

### **6.18 Unscheduled Visits**

Should patients require an unscheduled visit, the visit must be recorded in the patient's medical record and the eCRF, along with any assessments that were performed at the visit.

## 6.19 Early Termination Visit

Should a patient withdraw consent or be withdrawn from the study for any reason after randomization, every effort should be made to schedule a final visit, during which the following assessments should be completed in the order listed, if possible:

- Administer ACQ
- Review and record changes in concomitant medications
- Complete physical examination
- Vital sign measurements
- Record weight
- 12-lead ECG
- FeNO testing (recommended to be performed before spirometry)
- Spirometry (Pulmonary function tests)
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample
- PD blood sample
- ADA, NAb blood sample
- Urine pregnancy test for female patients of childbearing potential
- AE review and recording (Note: If the patient is being withdrawn due to asthma exacerbation, details of the exacerbation must be captured in the relevant asthma exacerbation source document and eCRF)
- Administer Healthcare Resource Utilization Questionnaire
- Collect and review diary and pulmonary function device data
- Injection site assessment

## 7.0 STUDY ASSESSMENTS

### 7.1 Demographic Data and Medical History

Demographic data regarding age, sex, race and ethnicity will be collected.

Medical history and demographics will be obtained at Screening (Visit 1).

A complete medical and surgical history will include evaluation for past or present cardiovascular, respiratory, ophthalmic, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatologic, psychiatric, genitourinary, musculoskeletal, medication, and surgical history, or any other diseases or disorders. The patient's medical history should be evaluated by the Investigator for clinical significance and re-reviewed at the Baseline visit (Visit 2).

## 7.2 Physical Examination

All full physical examinations will be performed by a physician, physician assistant, or nurse practitioner and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, thyroid, skin, cardiovascular system, respiratory system, lymph nodes, musculoskeletal, abdominal system, fundoscopy (optional), nervous system, and extremities.

Full physical examinations will be conducted at the following times:

- Screening (Visit 1)
- End of Study (Visit 17)
- Early Termination Visit

Brief focused physical examinations will be performed by a physician, physician assistant, or nurse practitioner and will assess the following: general appearance, eyes, lungs, and lymph nodes.

Brief focused physical examinations will be conducted at all visits where the full physical examination is not required.

## 7.3 Vital Sign Measurements

Blood pressure and pulse rate will be measured in a semi-supine or sitting position after the patient has rested for at least 5 minutes. Body temperature and respiratory rate will also be measured.

Vital signs will be measured at all clinic visits.

## 7.4 Weight and Height

Height and body weight will be measured at Screening (Visit 1). Weight will be measured and recorded again at Visits 2, 9, 15 and 17, or at the Early Termination Visit if the patient withdraws from the study.

## 7.5 Electrocardiogram

Standard 12-lead ECG recordings will be measured at the following time points:

- Screening (Visit 1)
- Visit 2 (Day 1)
- Visit 9 (Week 12)
- Visit 15 (End of Treatment)
- Visit 17 (End of Study)
- Early Termination Visit

The following parameters will be recorded:

- Rhythm
- Ventricular rate

- PR interval
- QRS duration
- QT
- QTcF

The Investigator will be responsible for reviewing the ECG to assess whether it is within reference limits and to determine the clinical significance of the results. The Investigator must sign and date all ECG printouts to indicate their review of clinical significance. A copy of the ECG assessment must be kept in the patient's file at the site. Note: The QTcF will be centrally calculated for standardization of reporting across all centers.

## 7.6 Safety Laboratory Tests

Standard laboratory hematology, serum chemistry, urinalysis, and hepatitis and HIV screening will be completed by Eurofins Central Laboratory.

**Hematology:** complete blood count to include red cell count, hemoglobin level, hematocrit level, white cell count with differential, and platelet count.

**Serum chemistry:** blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin, sodium, potassium, calcium, chloride, bicarbonate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), creatine phosphokinase (CPK), albumin, total protein, total cholesterol, triglycerides, C-reactive protein (CRP), and glucose.

**Urinalysis:** pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, leucocytes, and specific gravity; microscopic analysis if abnormal.

Hematology, serum chemistry, and urinalysis will be performed at the following times:

- Screening (Visit 1)
- Visits 2, 3, 5, 7, 9, 11, 13, 15 (End of Treatment), 16, and 17 (End of Study)
- Early Termination Visit

**Hepatitis and HIV Screening:** Hepatitis screen will assess HBsAg or HBcAb and HCVAb. An HCV viral load test is to be carried out if HCVAb is positive. The patient should be excluded from the study in case of positive HCV viral load test result. If the HCV viral load test result is negative, the patient can be enrolled in the study. *Note: Patients who test positive for HBcAb, negative for HBsAg and subsequently confirmed positive for HBsAb, indicating resolved natural infection (confirmed by negative HBV-DNA), may participate. Patients with positive HCV may participate if subsequent viral load is confirmed negative.*

**Additional Testing.** Additional and repeat testing for any safety parameter may be performed at the discretion of the Investigator in the interests of patient safety. If emergency testing is needed or a laboratory test is not available in the central lab, a local lab may be used. All laboratory test results should be recorded in the medical record and captured in the EDC under adverse event if possible.

As specified in the laboratory manual, all laboratory safety tests will be performed by Eurofins Central Laboratory. Details of all methodology and reference ranges are provided in the laboratory manual.

It is the responsibility of the Investigator to review and sign all lab reports, indicating the clinical significance of each abnormal/flagged value. In general, and as determined by the Investigator, abnormal clinically significant findings should be associated with an item recorded in the medical history or an AE.

## 7.7 Pregnancy Test

A pregnancy test will be performed for female patients of childbearing potential at the following times:

- Screening (Visit 1) – blood test
- Visits 2, 5, 7, 9, 11, 13, 15 (End of Treatment), 16, and 17 (End of Study) – urine test
- Early Termination Visit – urine test

Additional or more frequent pregnancy testing may be performed if required by local regulations.

## 7.8 Efficacy Assessments

### 7.8.1 Fractional Expired Nitric Oxide (FENO)

Fractional expiratory nitric oxide (FENO) will be measured using a NIOX™ system (Aerocrine, Solna, Sweden), or equivalent device. It is recommended that FENO testing be performed before spirometry after 1 hour fasting. Repeated, reproducible exhalations should be performed to obtain at least two NO plateaus that agree within 10% of each other. Record the lower of the two values in the eCRF.

FENO will be measured at the following time points:

- Screening (Visit 1)
- Visits 2, 3, 4, 5, 7, 9, 11, 13, 15, 16, 17
- Early Termination Visit

### 7.8.2 Daily Diary of Symptoms

Patients will be required to keep a diary of asthma symptoms twice daily via a symptom diary. The purpose of the diary is to record the impact of asthma on daily activities. The scoring system is described below. *Note: For the purposes of this study, “AM Questions” are those defined as being answered by the patient in the morning upon waking (ie, referring to the previous ~12 hours, or overnight symptoms). “PM Questions” are defined as those questions answered by the patient in the evening before retiring (ie, referring to the previous ~12 hours, or during the day when the patient was awake).* The Investigator should regularly review the diary and discuss any concerns over symptom changes with the patient. Programmed alarms will be programmed to encourage patients to contact the clinic if their symptoms worsen to indicate a possible exacerbation of their asthma.

## AM QUESTIONS:

### 1. How many puffs of rescue inhaler (albuterol/salbutamol) did you use last night?

[Patient will type in the number of puffs]

**2. How many times did you awaken due to asthma last night?**

- 0 Did not awaken due to asthma
- 1 Awoke once due to asthma
- 2 Awoke twice due to asthma
- 3 Awoke three times due to asthma
- 4 Was not able to sleep at all due to my asthma

**PM QUESTIONS:****1. How many puffs of rescue inhaler did you use today?**

[Patient will type in the number of puffs]

**2. Describe your asthma symptoms today.**

- 0 No noticeable symptoms of asthma
- 1 Mild asthma symptoms, barely noticeable
- 2 Asthma symptoms with exercise/exertion
- 3 Asthma symptoms with mild exertion
- 4 Almost constant difficulty breathing due to my asthma

**3. Were your daily activities affected by your asthma today?**

- 0 No effect of asthma on my daily activities
- 1 Activity was normal and only mildly affected by my asthma
- 2 Activity was normal but moderately affected by my asthma
- 3 Asthma symptoms limited my activity to a significant degree
- 4 Asthma symptoms severely restricted my daily activities

**4. Did you take your asthma controller (corticosteroid) medication today? Y/N****7.8.3 Daily Pulmonary Function Tests (at Home)**

The patient will be required to perform spirometry testing (PEF and FEV<sub>1</sub>) at home twice daily and to record the results using the pulmonary function test device dispensed at Visit 1. Programmed alarms will signal the patient to contact the clinic if lung function indicates the onset of a possible exacerbation.

#### **7.8.4 Pulmonary Function Tests (in Clinic)**

Spirometry (PEF, FVC, and FEV<sub>1</sub>) will be performed according to ATS ERS Standardization of Spirometry (2019), with equipment operated by trained clinical staff. In addition, reversibility testing will be performed at Visit 1 (Screening). Reversibility testing involves the measurement of FEV<sub>1</sub> before and 15 to 30 minutes after receiving up to 4 puffs of a SABA, preferably albuterol/salbutamol. The percentage reversibility is calculated as the improvement in absolute FEV<sub>1</sub> following bronchodilation.

Pulmonary function will be performed at the following time points:

- Screening (Visit 1)
- Visits 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 16 and 17
- Early Termination Visit and unscheduled visits

Reversibility testing will be done only during Screening (Visit 1). Patients need to have an airway reversibility of at least 12% to be eligible for the study.

#### **7.8.5 Asthma Control Questionnaire-**

The validated Asthma Control Questionnaire test will be used to evaluate patients' level of asthma control. This questionnaire will be completed by the patient at the following timepoints:

- Screening (Visit 1)
- Visits 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17
- Early Termination Visit

#### **7.8.6 Healthcare Resource Utilization Questionnaire**

The Healthcare Resource Utilization Questionnaire (Appendix E) will be used to evaluate the patients' need for medical services related to symptoms of their asthma. This questionnaire will be completed by patients at the following timepoints:

- Visits 2, 5, 7, 9, 11, 13, 15, 17
- Early Termination Visit

#### **7.8.7 Pharmacodynamic Endpoints**

Blood will be collected from patients throughout the study for measurement of biomarkers of inflammation associated with asthma including:

- Visits 2, 3, 5, 9, 15, 17
- Early Termination Visit

#### **7.8.8 Pharmacokinetic Assessments**

Whole blood for plasma CBP-201 concentrations will be obtained at the following visits to characterize the pharmacokinetics of the drug at steady-state and to characterize the return to baseline after treatment stops.

- Baseline (Visit 2)
- Visits 2, 3, 5, 9, 11, 15, 16, 17

- Early Termination Visit

### 7.8.9 Blood Volumes

The approximate blood volumes to be collected for safety labs, pregnancy, PK, PD, ADA are given in Table 2. These volumes may vary slightly based on regional differences in standard tube sizes and test requirements. Minor adjustments should not be considered protocol deviations. Maximum number of samples and total volumes over the 32-week study are estimates for safety consideration and should not be considered absolute requirements.

**Table 2: Blood Volumes**

| Assessment |              | Sample Volume (mL) | No. of Samples | Total Volume (mL) |
|------------|--------------|--------------------|----------------|-------------------|
| Safety     | Hematology   | 3                  | 11             | 33                |
|            | Biochemistry | 7.5                | 11             | 82.5              |
| HIV/HBsAg  |              | 5-7                | 1              | 5-7               |
| Pregnancy  |              | 5-7                | 1              | 5-7               |
| PK         |              | 5-7                | 8              | 40-56             |
| PD         |              | 5-7                | 6              | 30-42             |
| ADA/NAb    |              | 3-5                | 5              | 15-25             |

## 8.0 REPORTING ADVERSE EVENTS

### 8.1 Definitions

#### 8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient during a clinical study, whether or not it is related to the investigational product, at any time after the patient signs the ICF until Visit 17 (End of Study) or an Early Termination Visit, whichever occurs first.

**The term “asthma exacerbation” is broad and may be considered a collection of underlying signs and symptoms of worsening asthma. Major signs and symptoms associated with the asthma exacerbation (e.g., wheezing, dyspnea, coughing, chest tightness) must be documented on the AE page.** In addition, because exacerbation is a secondary endpoint of the study, more details about each exacerbation will be captured on a separate source document and the eCRF Asthma Exacerbation Form.

#### 8.1.2 Serious Adverse Event

An adverse event is considered “serious” if it:

- Results in death;
- Is life-threatening: when the patient is, in the opinion of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include an event that hypothetically might have caused death if it were more severe;
- Requires hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability or incapacity (ie, substantial disruption of a person's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect in the offspring of a patient;
- Is a medically important event, based upon the medical judgment of the Investigator, that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility. 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 in the absence of a precipitating clinical AE is not itself an SAE. Examples include optional admission for elective surgery, administrative admission (for a yearly physical or regular diagnostic procedure not associated with an AE), or admission for treatment of a pre-existing condition not associated with the development of a new AE or the worsening of a preexisting condition.

## **8.2 Eliciting Adverse Event Information**

The period of observation for AEs and SAEs extends from the time the patient signs the ICF until exit from the study. At each study visit patients will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the source document and AE eCRF (eg, laboratory values, physical examination findings, medical history, ECG changes), or other documents (eg, patient diaries) that are relevant to patient safety. Adverse medical conditions present at Baseline or since last assessment which become worse following exposure to study drug should be considered AEs. Any laboratory values that emerge or worsen since the last laboratory assessment and are deemed clinically significant by the Investigator should be considered AEs.

## **8.3 Adverse Event Reporting**

Both AEs and SAEs will be recorded from the time the patient signs the ICF until Visit 17 or Early Termination Visit, whichever occurs first. All AEs must be fully recorded into the source documents throughout the entire study period and will be transcribed into the AE eCRF, whether or not they are considered to be drug related.

Signs and symptoms of each AE should be described in detail, including

- onset time and date,
- offset time and date,
- severity (mild, moderate, severe, potentially life-threatening, death),
- relationship to study drug (related, not related),
- action taken (dose not changed, drug interrupted, drug withdrawn, not applicable, unknown), and

- outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, resolved with sequelae, fatal, unknown).

Adverse events should be followed until the event is resolved and/or stabilized. In the event a patient will not be returning to the clinical site, the outcome of this event will be recorded as lost to follow-up until an adequate medical explanation is available, whether the event is considered related to study drug. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution or stabilization. Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) will be used to code AEs and medical history. In addition, the World Health Organization Drug Dictionary (WHODrug) will be used to code medication usage.

Any medical condition that is present at the time the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

#### 8.4 Assessment of 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 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.

#### 8.5 Assessment of 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.**

## 8.6 AE of Special Interest (AESI)

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 notification by the Investigator to the Sponsor by email is required. Such events may require further investigation in order to characterize and understand them. These events should be marked "AESI" in the EDC. Adverse events of special interest may be added or removed during a study by protocol clarification note or amendment.

*Conjunctivitis and keratitis* have been subjects of interest in the dupilumab experience. [Akinlade et al 2019](#) reported that in the combined dupilumab experience in atopic dermatitis patients (n=1047) there were a total of 90 (8.6%) 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  $\leq 0.5\%$  of the dupilumab combined group vs.  $\leq 0.3\%$  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.

This pattern was not observed in dupilumab studies in other indications including asthma and chronic rhinosinusitis with nasal polyps.

Due to the dupilumab experience in atopic dermatitis, ophthalmic adverse events of "conjunctivitis" and "keratitis" will be considered AEs of special interest and may be evaluated by an ophthalmologist if deemed advisable by the Investigator or Sponsor. The appropriate treatment should be rendered until resolution.

**Other.** In addition to conjunctivitis and keratitis, the following AE's will also be categorized as AESI's: anaphylaxis, injection site reactions lasting longer than 24 hours, AST/ALT elevated  $>5X$  ULN, parasitic and opportunistic infections, pregnancy and symptomatic overdose.

**Anaphylaxis** will be defined by a collection of symptoms described by Sampson et al. 2006 and provided below:

*Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:*

*1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:*

*a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced Peak Expiratory Flow [PEF], hypoxemia)*

*b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)*

*2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*

*a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)*

*b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*

*c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)*

*d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)*

*3. Reduced BP after exposure to known allergen for that patient (minutes to several hours); systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.*

***Injection Site Reaction*** assessment of the previous injection will be done prior to dosing and again following the new injection prior to release of the patient from the clinic. An assessment tool is provided in the Appendix as an aid in the assessment of common symptoms of injection site reaction. The use of the assessment tool is encouraged but the Investigator may use their own judgement and description of symptoms in the assessment of injection sites following administration of IMP. An Injection Site Reaction should be reported as an Adverse Event if the Investigator judges the reaction as clinically significant. As a general guidance, a parameter grade of less than 2 is generally considered not clinically significant but the Investigator should use their judgement in the reporting of AEs. If the AE of Injection Site Reaction lasts longer than 24 hours, it will be considered an AESI.

***Parasitic or Opportunistic Infections*** should be considered. Questions concerning whether or not an infection is considered an opportunistic infection may be discussed with the Medical Monitor. The Investigator may also refer to Winthrop et al. 2015 for guidance in reporting of opportunistic infections.

## **8.7 Mandatory Early Treatment Discontinuation**

Using CTCAE Version 5.0, subjects who develop any related grade 2 or higher cardiovascular, respiratory or hematologic (example eosinophilia) 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.

## 8.8 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.

**All SAEs must be reported immediately (within 24 hours of discovery) by email to the CRO with copy to the Sponsor:**

**SAE Reporting email: [NorthAmerica\\_Medical@Parexel.com](mailto:NorthAmerica_Medical@Parexel.com)**

**Copy to Sponsor: [CBP-201clinical@connectpharm.com](mailto:CBP-201clinical@connectpharm.com)**

**Parexel Safety SAE Reporting Fax Number: +1 781-434-5957**

**Parexel Safety Reporting Help Line: +1 781-434-5010**

**24/7 Emergency Sponsor contact: +1 510-520-3361**

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.

### **8.8.1 Suspected Unexpected Serious Adverse Reactions**

Serious AEs and suspected unexpected serious adverse reactions (SUSARs) are not treated differently until an SAE is determined to be a SUSAR. The Investigator will report all SAEs to the Sponsor within agreed timelines.

An AE is “unexpected” only if its nature and severity are not consistent with the information provided by the Sponsor about the medicinal product. In the case of a product with a marketing authorization, this information is found in the summary of product characteristics; in the case of any other investigational medicinal product, it is found in the Investigator’s Brochure relating to the trial in question. There is limited clinical experience with CBP-201 in asthma patients. Because dupilumab is a marketed product for asthma in the same class that binds to the same target (IL4Ralpha), SAEs not currently reflective of safety presented in the latest available version of the dupilumab package insert, from the Investigator’s Brochure, or SAEs not consistent with the medical history of the patient will be considered as SUSARs.

A SUSAR that is fatal or life-threatening must be reported to the IRB/EC, the US Food and Drug Administration (FDA), and/or other competent authorities within 7 days after the Sponsor becomes aware of the event. The Investigator is responsible for notifying the IRB/EC and the Sponsor is responsible for notifying the competent regulatory authorities. Any additional information must be reported within 8 days of sending the first report.

A SUSAR that is not fatal or life-threatening must be reported to IRB/EC, and/or other relevant competent regulatory authorities as soon as possible (within 15 days) after the Sponsor becomes aware of the event. The Investigator is responsible for reporting to the IRB/EC and the Sponsor is responsible for notifying the competent regulatory authorities.

In addition, SUSARs will be reported to any IRBs/ECs and Principal Investigators as required by local law.

Periodic and annual reporting will be performed per country-specific guidelines.

### **8.9 Pregnancy Reporting**

For the purposes of this study, pregnancy of any female patient will be considered an AESI and should be reported within 24 hours to the medical monitor and Sponsor on the Pregnancy Form. The patient will be asked to provide information on the outcome of the pregnancy, including premature termination (elective abortion). If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion), the Investigator should follow the procedures for reporting SAEs. Pregnancy itself is not an SAE. Female patients becoming pregnant during the study and after randomization must be immediately withdrawn from study treatment and followed to resolution, which includes birth or termination of the pregnancy. Every attempt should be made to follow the pregnancy to completion. If possible, births will be followed by the Investigator for 8 weeks for observation of possible congenital abnormalities. Pregnancies of a male patient’s partner will not be considered an AE and the male patient should not be withdrawn from the study. If a male patient’s partner becomes pregnant during this time period (from first dose until 8 weeks after the last dose), the Investigator will inform the Sponsor, and the IRB or EC, as appropriate, as well as providing the appropriate medical follow-up if agreed to by the partner.

## 9.0 STATISTICAL METHODS

Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate statistical analysis plan (SAP).

### 9.1 Sample Size

The sample size is calculated based on a 2-sided 2-sample t-test with a 5% significant level ( $\alpha = 0.05$ ) for the comparison of CBP-201 300 mg Q2W with placebo on absolute change from baseline in prebronchodilator (trough) FEV<sub>1</sub> at Week 12.

A sample size of 258 patients (randomization ratio of 1:1:1; 86 patients in each CBP-201 150 mg Q2W, CBP-201 300 mg Q2W, and placebo) will provide 80% power to assess superiority for change in prebronchodilator (trough) FEV<sub>1</sub> at Week 12 assuming a 0.15 L difference between CBP-201 300 mg Q2W and placebo, and will allow analysis of the safety and tolerability of CBP-201. The treatment difference of 0.15 L is assumed using the least-squares mean difference versus placebo for change from baseline in prebronchodilator (trough) FEV<sub>1</sub> at Week 12 from the phase 3 dupilumab study assessing the efficacy of dupilumab in patients with uncontrolled moderate-to-severe asthma (Castro et al, 2018). The assumed common standard deviation is 0.35 L, which is derived using the standard error for estimated least-squares change from baseline in prebronchodilator (trough) FEV<sub>1</sub> at Week 12 from the same phase 3 dupilumab study (Castro et al, 2018). These estimates are based on data published in Castro et al. 2018. To accommodate a potential dropout rate of 15%, the planned total sample size is 306 (102/arm).

### 9.2 Analysis Sets

Five populations will be defined: Randomized Set, Full Analysis Set (FAS), Per Protocol (PP) Set, Safety Analysis Set, and PK Set.

#### **Randomized Set**

The Randomized Set includes all patients who are randomized to treatment.

#### **Full Analysis Set (FAS)**

The Full Analysis Set (FAS) consists of randomized patients who receive at least 1 dose of study medication. These patients are assigned based on the treatment group to which they were randomized.

Patients in this set will be analyzed according to their randomized treatment assignment, regardless of treatment received. The efficacy endpoints will be primarily based on the FAS.

#### **Per Protocol (PP) Set**

The PP Set consists of all FAS patients without major protocol deviations.

#### **Safety Analysis Set**

The analysis population for the safety endpoints will be the Safety Analysis Set. The Safety Analysis Set consists of all randomly assigned patients who receive at least 1 dose of study

drug. These patients will be analyzed according to their actual treatment received, regardless of the randomized treatment.

### **Pharmacokinetic (PK) Set**

The PK Set consists of all randomly assigned patients who receive at least 1 dose of study drug and have at least 1 post-dose PK blood sample collected. The PK set will be used for all PK analyses.

## **9.3 Statistical Methodology**

All statistical tests will be 2-sided with a 5% significance level ( $\alpha = 0.05$ ), unless otherwise stated. Continuous variables will be summarized by descriptive statistics, including the number of patients, mean, standard deviation (SD), median, interquartile range (25<sup>th</sup> quartile, 75<sup>th</sup> quartile), minimum, maximum, and the geometric mean, where appropriate. Categorical variables will be presented with the frequency and percentage of patients in each corresponding category by treatment group. Specific statistical methodology will be provided in the SAP to be completed before the unblinding of the study data.

## **9.4 Pharmacokinetic Analysis**

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

Additional sampling will be obtained after the last treatment dose, as noted in the schedule of assessments, to characterize the return to baseline.

The details of PK analysis will be reported in a separate PK analysis report.

## **9.5 Efficacy/Pharmacodynamic Analysis**

### **9.5.1 Primary Analysis**

The primary analysis will be performed using the analysis of covariance (ANCOVA) model with the absolute change from baseline to Week 12 in prebronchodilator (trough) FEV<sub>1</sub> as the dependent variable and treatment group (three levels), FEV<sub>1</sub> at Baseline and the randomization stratification factors as fixed effects. Summaries for the results of the primary analysis will include least-squares-means point estimates of the absolute change from Baseline for each treatment arm. The 2-sided 95% CI and associated p-value will be provided for the difference between the least-squares means for each CBP-201 treatment group and placebo.

Conclusion for the primary efficacy hypothesis of different efficacy of each CBP-201 group compared with placebo at prebronchodilator (trough) FEV<sub>1</sub> will be made using a two-sided test at the  $\alpha = 0.05$  level of significance. The primary efficacy analysis will use the FAS.

### **9.5.2 Secondary Analysis**

The analysis for secondary endpoints of absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, 8, and 24 will be performed using a mixed model for repeated measures (MMRM) using the FAS. The MMRM model will be fit with the absolute change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> as the dependent variable, and it will include treatment group (three levels), FEV<sub>1</sub> at Baseline and the randomization stratification factors, and treatment-by-visit interaction as fixed effects. The visit will be treated as a categorical variable.

Similar MMRM models for percent change from Baseline in prebronchodilator (trough) FEV<sub>1</sub> for will be conducted for percent change from Baseline to each time point, Weeks 1, 2, 4, 8, 12 and 24 in FEV<sub>1</sub>, and change from baseline in other lung function measurements such as percentage predicted FEV<sub>1</sub>, morning and evening PEF and FEV<sub>1</sub>.

Time to exacerbation is defined as the time from the first dose to the first start time of exacerbation. The median of the time to exacerbation and the corresponding 95% CI for each treatment group will be estimated using the Kaplan-Meier (K-M) method. The K-M plot for time to exacerbation will be generated and plotted over the 24-week treatment period to provide a visual description of the time to exacerbation over time. Log-rank test will be performed to compare the event free distribution between each CBP-201 group and placebo group.

Proportion of patients with  $\geq 1$  loss of asthma control event during the 24-week treatment period will be calculated with the corresponding 95% CI by treatment group. The difference between each CBP-201 group and placebo group and the corresponding 95% CI will be calculated as well. Chi-square test or Cochran-Mantel-Haenszel test will be performed to compare the proportion between each CBP-201 group and placebo group.

All secondary analyses will be conducted using two-sided tests at the  $\alpha=0.05$  level of significance. Details of the secondary analyses will be included in the SAP.

### **9.5.3 Exploratory Analyses**

Exploratory clinical efficacy endpoints will include asthma exacerbation rate, and change from baseline at Weeks 1, 2, 4, 12, and 24 in the following symptoms as captured in the diary: weekly mean asthma symptom score (night-time), weekly mean rescue medication use, number of nights with awakening due to asthma, weekly mean number of night-time awakenings due to asthma, healthcare resource utilization questionnaire (HRUQ), and asthma control questionnaire (ACQ) score. All these exploratory endpoints will be summarized using descriptive statistics or counts and percentages of patients as appropriate for each of the three treatment groups based on the FAS.

Exploratory pharmacodynamic endpoints will also be analyzed, including change from baseline in FENO, blood levels IgE, blood levels of thymus and activation-regulated chemokine (TARC), peripheral eosinophil counts, and other markers of atopic inflammation in the blood (periostin, CRP, eotaxin-3, and eosinophil cationic protein). All these exploratory pharmacodynamic endpoints will be summarized using descriptive statistics based on the FAS.

### **9.5.4 Multiplicity Considerations**

No multiplicity adjustment is considered in this study.

## **9.6 Safety Data Analysis**

All safety analyses will be based on the Safety Analysis Set.

Summaries will be provided by scheduled visit and time point or for the entire treatment period and follow-up period, as appropriate. Quantitative data collected at unscheduled times will be listed but will not be included in summaries. Categorical data collected at unscheduled times (i.e., ECG finding categories) will not be included in summaries by time point but will be included in summaries of findings during the entire treatment period.

Safety endpoints to be summarized include adverse events, vital signs (blood pressure, heart rate, respiratory rate, and temperature), ECG parameters, and safety laboratory data (hematology, serum chemistry, and urinalysis).

Two approaches will be used for handling safety data occurring after the initiation of rescue therapy. The first approach will exclude all data following the initiation of rescue, to avoid the confounding influence of the rescue therapy. The second approach will include data following the initiation of rescue therapy. For the overall study analyses, the “including rescue” approach will be considered primary for all safety endpoints.

#### **9.6.1 Analysis of Exposure to Study Drug**

Extent of exposure will be calculated from data collected in the study drug administration page of the CRF and summarized by treatment group. The duration of study drug exposure will be calculated using the first and last day of study drug dosing. Reasons for study drug discontinuation will be summarized. For each patient, treatment compliance over the interval from first to last dose will be calculated from data collected in the study drug administration and drug accountability pages of the eCRF. Treatment compliance will be summarized by actual treatment received.

#### **9.6.2 Adverse Event Data**

Adverse events will be coded to the preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) available at the beginning of the trial and will keep using that version throughout the study unless there is a rationale for change. Treatment-emergent adverse events (TEAEs) are defined as any AEs that occurred or worsened during the treatment period and follow-up period, whether or not considered related to treatment. The incidence of TEAEs, including SAEs, injection site reaction, and AESIs, will be presented overall, by system organ class (SOC), and by preferred term (PT) for each treatment group. Incidence of AEs by severity and relationship to study drug will also be presented. Deaths, SAEs, AESIs and adverse events resulting in discontinuation from the study or discontinuation from study treatment will be summarized.

For AESI, the percentage of patients with incident AE, the risk difference, its 95% confidence interval, and p-value will be provided. The confidence intervals and p-values are not adjusted for multiplicity and therefore must be considered accordingly. The requirement will be at least 4 patients in any treatment arm. The cut-off of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and so adds little to the interpretation of potentially meaningful differences.

A listing will be provided for all patients who experience a TEAE, SAE, and discontinued study treatment or study prematurely because of AEs, and temporarily interrupted study treatment because of AEs. AESIs (Section 8.6) will also be listed.

#### **9.6.3 Laboratory Data**

Laboratory values, changes from Baseline, and values relative to normal ranges will be summarized. Reference ranges provided by the laboratory for each test will be used to evaluate the clinical significance of laboratory test results. Values failing outside the relevant reference

range will be flagged, as appropriate, in the data listings. Separate listings will be provided for abnormalities in clinical laboratory test results.

#### **9.6.4 Vital Signs Data**

Systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate, and body temperature values at each visit and time point and changes from Baseline at each visit and time point after first dose will be summarized.

#### **9.6.5 ECG Data**

Rhythm, ventricular rate, QT, QTcF, PR, and QRS values at each time point and changes from Baseline at each time point after first dose will be summarized. Counts and percentages will be shown for SAP-specified value and change from baseline categories of special interest.

A listing of patients with extreme values or changes, as specified in the SAP (i.e., values of QTcF > 500 msec, QTcF increases from baseline > 60 msec) will be provided.

### **9.7 Demographic and Medical History**

Demographic characteristics (i.e., gender, age, weight, height, ethnicity) and medical history with disease-relevant baseline characteristics (i.e., pulmonary function, number of exacerbations in the past year, prior asthma medication use) will be summarized on both the Safety and the FAS by treatment group. All other baseline characteristics will be summarized as well.

### **9.8 Analysis of Concomitant Medication Use**

Medication names will be coded according to the World Health Organization Drug Dictionary (WHO-DD). The prior medications summaries will include all medications stopped before the date of the first study drug dose. The summary of concomitant medications will comprise all medications taken during the treatment period, including medications ongoing at entry. Prior and concomitant medications will be summarized overall and by the drug classification using the Safety Analysis Set.

### **9.9 Protocol Violations**

A list of patients with protocol violations will be completed based on entry criteria and violations from study conduct and assessments. The number of patients with major protocol violations will be summarized by treatment group.

### **9.10 Missing Data**

For the primary analyses, missing values of prebronchodilator (trough) FEV<sub>1</sub> will be imputed by using multiple imputation (MI) for Week 12 at which no value is observed. MI will be performed under missing at random (MAR) assumption. The MI model will include treatment, FEV<sub>1</sub> at baseline, the randomization stratification factors, and prebronchodilator (trough) FEV<sub>1</sub> at Weeks 1, 2, 4, and 8. Primary analysis method will be repeated on multiply imputed datasets.

Missing data from patients who discontinue study drug permanently or receive rescue medication in the CBP-201 arm will be assumed missing not at random (MNAR). Under MNAR assumption, imputation of missing data at Week 12 will be done using pattern mixture model-multiple imputation (PMM-MI), control-based PMM-MI and/or tipping point analysis. Primary analysis method will be repeated on multiply imputed datasets.

All these missing data imputation methods will be applied in primary analysis and included in sensitivity analysis (Section 9.11).

All secondary and exploratory efficacy analyses, as well as all safety analyses, will be conducted using available data with no imputation for missing values. Details on missing data imputation for primary analysis will be described in the SAP.

### **9.11 Sensitivity Analysis**

Sensitivity analyses will be conducted to confirm the robustness of the results for the primary analyses. These will include repeating the primary analysis described in Section 9.5.1 based on the Per Protocol (PP) Set, analysis for the primary endpoint using the MMRM model, pattern mixture model-multiple imputation (PMM-MI), control-based PMM-MI and/or tipping point analysis. Details will be described in the SAP.

## **10.0 DATA HANDLING AND QUALITY ASSURANCE**

### **10.1 Case Report Forms**

Study data is recorded using an eCRF via the Medidata RAVE Electronic Data Capture (EDC) system provided by the CRO.

Study data will be recorded in the eCRF by clinical research staff at each clinical site.

Study data will also be recorded on source documents maintained by clinical research staff at each investigative site. Source documents may include medical records, laboratory reports, patient diaries, ECG and spirometry printouts, consult notes, Investigator notes, and medical history data from a primary care physician, health care professional, or institution. Data recorded in source documents will be transcribed, where necessary and appropriate, into eCRFs by the clinical research staff at each investigative site. All source documents will be retained at the clinical site. Photocopies of completed source documents will be provided only if essential (ie, for regulatory purposes) at the request of the Sponsor or its designee.

The eCRFs must be kept in order and up-to-date so that they always reflect the latest observations on the enrolled patients.

Each patient's source documents should have the original signed ICF attached. When the study treatment is completed, the ICF should be kept with a copy of the completed eCRF in the appropriate file method provided, or with a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

All original signed laboratory reports must be available for review.

The eCRFs must be reviewed, authorized, and signed by the Investigator. The procedures and protocol for electronic signature, if applicable, will be provided to and discussed with the Investigator and training will be provided.

### **10.2 Monitoring of the Study**

The Parexel Clinical Monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the Monitor will visit the Principal Investigator or Sub-Investigator and study facility at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, facsimile, and letter. The Monitor will maintain current personal

knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Principal Investigator or Sub-Investigator and staff.

All aspects of the study will be carefully monitored, by Parexel and the Sponsor, for compliance with applicable government regulation with respect to current Good Clinical Practice (GCP) and standard operating procedures.

### **10.3 Inspection of Records**

The Principal Investigators or Sub-Investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the Principal Investigator or Sub-Investigator agrees to allow the Sponsor, representatives of the Sponsor, Parexel and relevant competent regulatory authorities access to all study records.

The Principal Investigator or Sub-Investigator should promptly notify the Sponsor, or its designee, of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Sponsor or its designee.

### **10.4 Study Record Retention**

Essential documents should be retained for at least 15 years after the end of the trial or 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Principal Investigator or Sub-Investigator or institution as to when these documents no longer need to be retained.

## **11.0 ADMINISTRATIVE CONSIDERATIONS**

The following administrative items are meant to guide the Principal Investigator or Sub-Investigator in the conduct of the trial but may be subject to change based on industry and government standard operating procedures or working practice documents or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

### **11.1 Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, competent regulatory authorities, or the IRB/EC.

The Principal Investigator or Sub-Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

## **11.2 Data and Safety Monitoring Board**

An independent Data Safety Monitoring Board (DSMB) will be set up to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and to make recommendations to the Sponsor concerning the continuation of the trial. The DSMB will be comprised of independent expert(s) in the clinical aspects of the disease/patient population being studied, one or more biostatisticians, and one or more investigators with expertise in current clinical trials conduct. These members may not be directly involved in the conduct of the blinded study.

A separate DSMB Charter document will outline the schedule of data review, define the deliberative process, any events that would trigger unscheduled reviews, stopping procedures that are consistent with the protocol, unmasking and voting procedures, and the contents of reports at the conclusion of each meeting, and how the DSMB will vote as to whether the study should continue without change, be modified or be terminated.

## **11.3 Institutional Review Board/Ethics Committee Approval**

Federal and national regulations and ICH guidelines require approval be obtained from an IRB/EC before participation of human patients in research studies. Before the study onset, the protocol, informed consent, advertisements to be used for patient recruitment, and other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/EC. Documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/EC approvals should be signed by the IRB/EC Chairman or designee and must identify the IRB/EC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

The Principal Investigator or Sub-Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/EC. The Principal Investigator or Sub-Investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

## **11.4 Modification of the Protocol**

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee.

Amendments to the protocol will be prepared by the Sponsor or its designee and must be submitted in writing to the Principal Investigator's or Sub-Investigator's IRB/EC for approval before patients being enrolled into an amended protocol or amended procedures applied to currently enrolled patients.

## **11.5 Informed Consent**

A written ICF in compliance with Title 21 of the Code of Federal Regulations (CFR) Part 50, current version of the Declaration of Helsinki; the current requirements of GCP (CPMP/ICH/135/95); and local regulations, whichever afford the greater patient protection, shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure involving risk to the patient. In addition, a separate ICF should be

obtained from each patient who chooses to participate in the genetic analysis as outlined within the protocol. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICFs (general and genetic) should be reviewed by the Sponsor or its designee, if appropriate, before IRB/EC submission. Once reviewed, the ICFs will be submitted by the Principal Investigator or Sub-Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICFs are revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his/her legal guardian will be given a full explanation of the study and allowed to read the approved ICFs. Once the Principal Investigator or Sub-Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF(s).

The Principal Investigator or Sub-Investigator shall provide an original or a copy of the signed ICF to the patient and/or legal guardian. An original form shall be maintained in the patient's medical records at the site.

## **11.6 Protocol Violations and Deviations**

The Principal Investigator, Sub-Investigator, or designee must document and explain in the patient's source documentation any deviation and violations from the approved protocol. The Principal Investigator or Sub-Investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to trial patients without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/EC for review and approval (if required), to the Sponsor or its designee for agreement, and to the regulatory authorities (if required).

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/EC and agreed to by the Principal Investigator or Sub-Investigator. Deviations usually have an impact on individual patients, or a small group of patients, and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when there is nonadherence to the protocol resulting in a significant, additional risk to the patient, when the patient or Principal Investigator or Sub-Investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and/or the patient was enrolled without prior Sponsor approval, or when there is non-adherence to competent authority regulations and/or ICH GCP guidelines.

The clinical monitor and site staff will document protocol violations and deviations throughout the course of the clinical trial. The monitor will notify the Principal Investigator or Sub-Investigators during a visit and document in writing all violations and deviations. The IRB/EC should be notified by site personnel of all protocol violations and any applicable protocol deviations according to their IRB/EC regulations in a timely manner.

## **11.7 Study Reporting Requirements**

By participating in this study, the Principal Investigator or Sub-Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Principal Investigator or Sub-Investigator agrees to submit annual reports to his/her IRB/EC as appropriate.

## 11.8 Financial Disclosure and Obligations

The Principal Investigators or Sub-Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the Principal Investigator or Sub-Investigators must provide to the Sponsor a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor CRO is financially responsible for further testing and/or treatment of any medical condition which may be detected during the Screening (Visit 1) process. In addition, in the absence of specific arrangements, neither the Sponsor nor CRO is financially responsible for further treatment of the patient's disease.

## 11.9 Investigator Responsibilities and Documentation

Before beginning the study, the Principal Investigator will be asked to comply with ICH E6 8.2 and Title 21 of the CFR and any local regulatory requirements by assuring responsibility for and providing the following procedures and essential documents, including, but not limited to:

- Conducting study according to current protocol approved by appropriate IRB or EC.
- Personally conducting study or personally supervising Sub-Investigators and other staff involved in study conduct.
- Ensuring all study staff are informed of their obligations to meet the Investigator commitments in Form FDA 1572 (US) or ICH E6.4 and other local regulations such as financial disclosure forms.
- Reading and understanding the current version of the CBP-201 Investigator's Brochure (version 5 or above).
- Obtaining IRB/EC review and approval for study (per 21 CFR 56 [US] and ICH E6.4).
- Ensuring IRB/EC provides initial and continuing review, and the approval of the study complies with relevant local regulations (per 21 CFR 56 [US] and ICH E6.4); promptly informing IRB/EC of changes in research activity or any unanticipated problems involving risk to patients.
- Making no changes to study without approval by Sponsor and IRB/EC review and approval (except when needed immediately to protect safety, rights, or welfare of study patients).
- Notifying study patients that CBP-201 is investigational; obtaining informed consent from each patient per relevant regulations (per 21 CFR 50 [US] and ICH E6.4).
- Informing Sponsor or designee of AEs during study (per 21 CFR 312.64 [US] and ICH E6.4); SAEs to be reported within 24 hours.
- Maintaining adequate and accurate records (per 21 CFR 312.62 [US] and ICH E6.4); make records available for inspection (per 21 CFR 312.68 [US] and ICH E6.4).
- Complying with all other pertinent requirements of 21 CFR 312 (US) and ICH E6.4.
- An original Investigator-signed Investigator Agreement page of the protocol

- Providing an IRB/EC-approved ICF, samples of site advertisements for recruitment, and any other written information regarding this study that is to be provided to the patient or legal guardians.
- Form FDA 1572 (US) or form with equivalent information, fully executed, and all updates on a newly executed Form FDA 1572 (US) or equivalent.
- Curriculum vitae (CV) for the Principal Investigator and each Sub-Investigator will be listed on Form FDA 1572 (US) or ICH E6.4 or local equivalent. Current licensure must be noted on the CV. These will be signed and dated by the Principal Investigators and Sub-Investigators at study start-up, indicating they are accurate and current.
- Providing financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54 (US) or relevant local equivalent.
- Providing laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493 (US) or relevant local equivalent.

### **11.10 Study Conduct**

The Principal Investigator agrees the study will be conducted according to the principles of the ICH E6 Guideline for GCP and the principles of the World Medical Association Declaration of Helsinki. The Principal Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

### **11.11 Financing and Insurance**

This study is funded by Suzhou Connect Biopharmaceuticals, Ltd. Insurance policies will be arranged at the time of study start, as required in each country in which the study is conducted.

### **11.12 Publications**

Following completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues. Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

### **11.13 Risk Mitigation and Safety Measures due to COVID-19 Pandemic**

Due to the COVID-19 pandemic, operational measures may be implemented to ensure a continued supply of medication, to perform efficacy assessments, and for adequate safety monitoring of patients. These measures may include remote study visits, home healthcare, handling of protocol deviations, and remote site monitoring.

Any protocol deviations due to COVID-19 restrictions will be documented in the EDC system.

Any protocol deviations that could potentially impact data analysis will be flagged and the handling of such deviations will be described in the Statistical Analysis Plan.

## **12.0 INVESTIGATOR'S STATEMENT**

I agree to conduct the study as outlined in the protocol entitled "A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Efficacy and Safety Study of CBP-201 in Patients with Moderate to Severe Persistent Asthma with Type 2 Inflammation" in accordance with the guidelines and all applicable government regulations including Part 54 of Title 21 of the CFR. I have read and understand all sections of the protocol, including Section 11.0 ADMINISTRATIVE CONSIDERATIONS.

**Protocol Version 4.0**

**Date: 04 May 2022**

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**Principal Investigator's Signature**

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**Date**

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**Printed Name**

### 13.0 REFERENCES

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Suzhou Connect Biopharmaceuticals, Ltd.  
Investigational Drug: CBP-201

Protocol CBP-201-WW002  
04 May 2022

## **APPENDICES**

### **APPENDIX A – ACQ (Questions 1-5 + 7)**

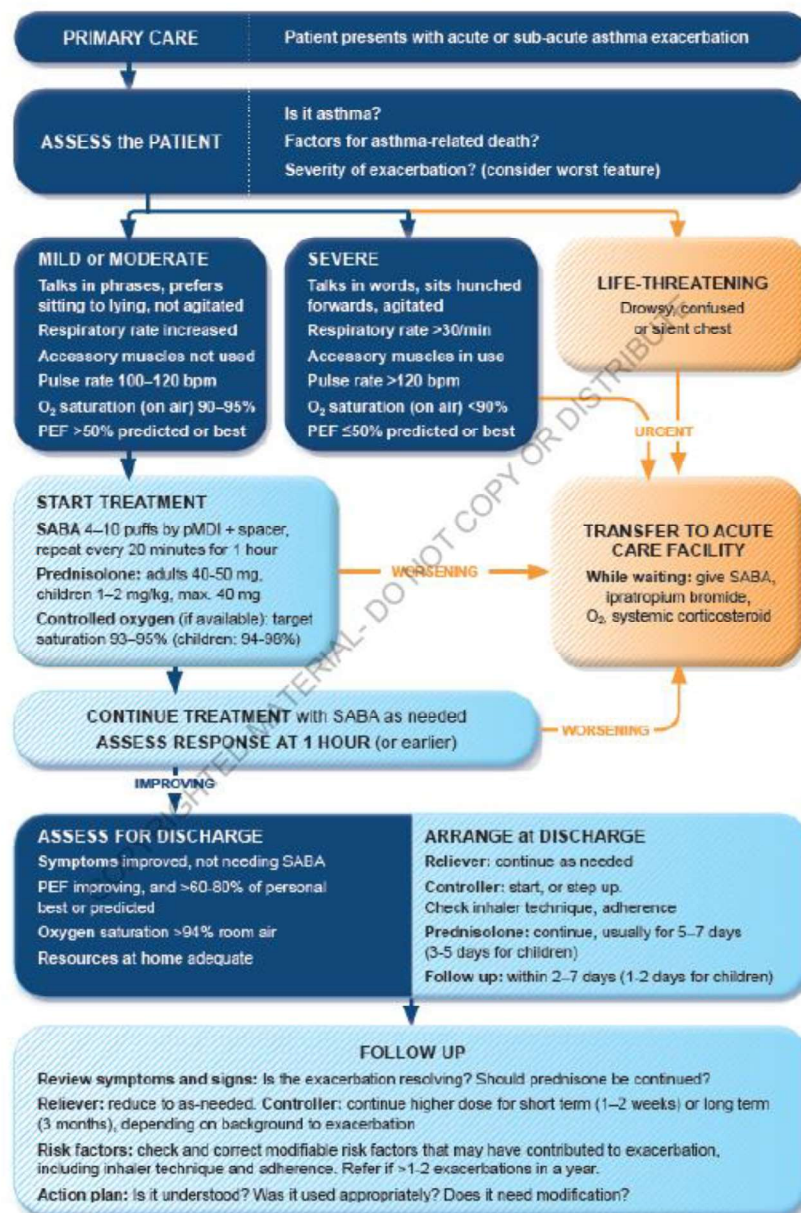
The example appendix was removed due to copyright restrictions. Please see Juniper EF et al. 2005 for details.

## APPENDIX B – GINA GUIDELINES FOR CLASSIFICATION OF EXACERBATION SEVERITY

### Global Initiative for Asthma (GINA) Guidelines

From GINA, rev. 2020 – Global Strategy for Asthma Management and Prevention

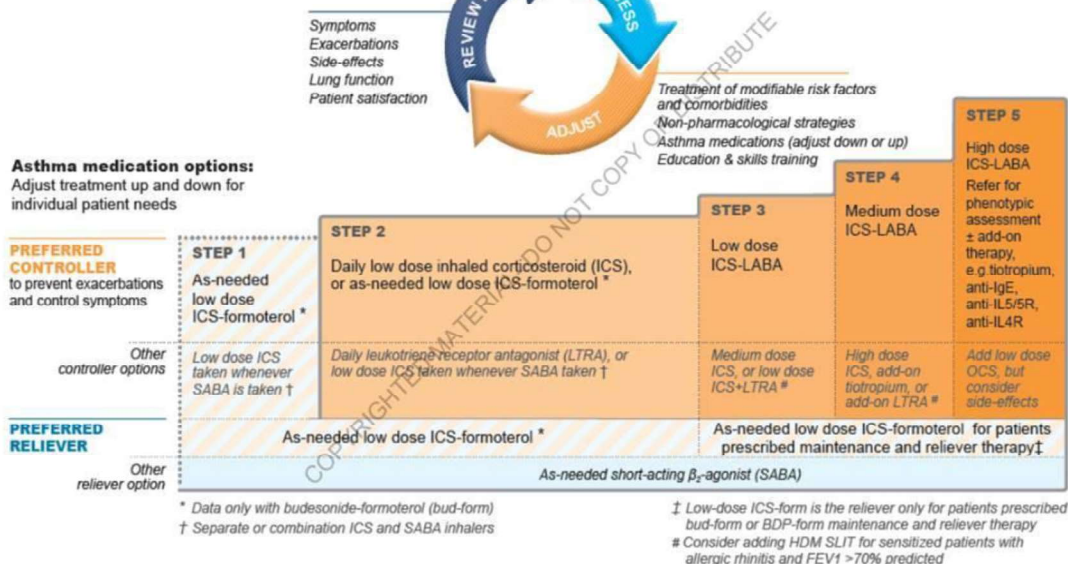
Box 4-3. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)



**APPENDIX C – GINA GUIDELINES FOR CLASSIFICATION OF ASTHMA****Global Initiative for Asthma (GINA) Guidelines**

From GINA, rev. 2020 – Global Strategy for Asthma Management and Prevention

Box 7A. The GINA asthma treatment strategy – adults and adolescents

**Adults & adolescents 12+ years****Personalized asthma management:**  
Assess, Adjust, Review response

See Box 8A for children 6–11 years. For more details about treatment recommendations, and for supporting evidence, and clinical advice about implementation in different populations see the full GINA 2020 report ([www.ginasthma.org](http://www.ginasthma.org)). For more details about Step 5 add-on therapies, see GINA 2019 Pocket Guide on Difficult to Treat and Severe Asthma, and check eligibility criteria with local payers.

**ASSESSING ASTHMA SEVERITY****How to assess asthma severity in clinical practice**

Currently, asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations.<sup>17,59,138</sup> It can be assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years.

Asthma severity can be assessed when the patient has been on controller treatment for several months.<sup>17,138</sup>

- **Mild asthma** is asthma that is well controlled with Step 1 or Step 2 treatment (Box 3-5, p.54), i.e. with as-needed ICS-formoterol alone, or with low-intensity maintenance controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones. For patients prescribed as-needed ICS-formoterol, the frequency of use that should be considered to represent well-controlled asthma has not yet been determined.
- **Moderate asthma** is asthma that is well controlled with Step 3 treatment e.g. low dose ICS-LABA.
- **Severe asthma** is asthma that requires Step 4 or 5 treatment (Box 3-5, p.54), e.g. high dose ICS-LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.<sup>138</sup> See Chapter 3E (p.94) for more detail about the assessment of patients with difficult to treat or severe asthma.

**APPENDIX D-Injection Site Assessment Tool**

The following Injection Site Assessment Tool is provided as an aid in the assessment of common symptoms of injection site reaction. The Investigator may use their own judgement and description of symptoms in the assessment of injection sites following administration of IMP. An Injection Site Reaction should be reported as an Adverse Event if the Investigator judges the reaction as clinically significant. A parameter grade of less than 2 is generally considered not clinically significant but the Investigator should use their judgement in the reporting of AEs. See section 8.6.

**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                                                               |

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Protocol CBP-201-WW002  
04 May 2022

## APPENDIX E- Healthcare Resource Utilization Questionnaire

Site Number: \_\_\_\_\_ Subject Number: \_\_\_\_\_ Visit Number / Name: \_\_\_\_\_

Name of Interviewer: \_\_\_\_\_

Administration Date: \_\_\_\_\_ Administration Time: \_\_\_\_\_

Instructions: The study coordinator or research nurse is to administer the Healthcare Resource Utilization Questionnaire as an interview with the subject since their last visit.

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1. How many times have you visited (in-person or telehealth) your usual healthcare provider for asthma since your last visit? Number of visits \_\_\_\_\_

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2. How many times have you visited an urgent care center for asthma since your last visit? Number of visits \_\_\_\_\_

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3. How many times have you visited an Emergency Department for asthma since your last visit? Number of visits \_\_\_\_\_

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4. How many days have you been hospitalized for asthma since your last visit? Number of days \_\_\_\_\_

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