CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate CBP-201 in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps

Product:	**CBP-201**
Protocol Number:	**CBP-201-WW003**
Version Number:	**3.0**
Date of Issue:	**21 December 2021**
Sponsor:	**Suzhou Connect Biopharmaceuticals Ltd.**

Confidentiality Statement

SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate CBP-201 in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps

PROTOCOL NUMBER: CBP-201-WW003

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 and Patients have 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.

DocuSigned by:
Jing Song
B3A2221CA5D342C...

12/27/2021

Jing Song, MD **Date**

Sr. Physician, Clinical Development
Suzhou Connect Biopharmaceuticals, Ltd.
Email: jsong@connectpharm.com

DocuSigned by:
Malinda Longphre
614A552BDA754A3...

12/23/2021

Malinda Longphre, PhD **Date**

Executive Director, Clinical Operations
Suzhou Connect Biopharmaceuticals, Ltd.
Mobile: +1 510 520 3361
Email: mlongphre@connectpharm.com

DocuSigned by:
Daniel Miconi
504E1184B4304D4...

12/27/2021

Daniel Miconi **Date**

Senior Manager, Clinical Operations
Suzhou Connect Biopharmaceuticals, Ltd.
Mobile: +1 707 870 5226
Email: dmiconi@connectpharm.com

SPONSOR Suzhou Connect Biopharmaceuticals, Ltd. Corporate Headquarters Science and Technology Park, East R&D Bldg, 3rd Floor, 6 Beijing West Road, Taichang, Jiangsu, China 215400 www.connectbiopharm.com Phone: +86 13910526977	**CRO:** Parexel International, LLC 8 Federal Street Billerica, MA 01821 *Contact details of the CRO Project Manager, Medical Monitor, and clinical team involved in this study are provided in the study contact list.*
SAFETY REPORTING AND QUERY LINE: Parexel International, LLC Phone: +1 781-434-5010 **24-HOUR SPONSOR CONTACT:** Suzhou Connect Biopharmaceuticals, Ltd. Phone: +1 (510) 520-3361	**PHARMACOKINETIC ANALYSIS:** P Less Than Dennis Fisher, MD 218 Castenada Avenue San Francisco, CA 94116 UNITED STATES Tel: +1 415 307-4791 Email: fisher@plessthan.com
CENTRAL LABORATORY: **Laboratory Contact USA:** Eurofins Central Laboratory Lisa Russell Knode Laboratory Manager 2430 New Holland Pike Lancaster, PA 17601 Phone number: +1 (717) 556 3851 FAX: +1 (717) 556 3888 Email: LisaRussellKnode@eurofinsUS.com	**BIOANALYSIS LABORATORY:** **Laboratory Contact PK (ex-China):** Syneos Health Mounia Khyari, Manager 2500 Einstein, Quebec (Quebec) G1P 0A2 CANADA Direct: +1 418 -527 -3067, Ext:5696 Mobile: +1 418 254 7107 Email: Mounia.khyari@syneoshealth.com

Laboratory Contact Europe: Eurofins Central Laboratory Tom de Kerf Manager Clinical Laboratory Bergschot 71 4817 PA Breda The Netherlands Phone number: +31 76 5737 306 E-mail: tomdekerf@eurofins.com	**Laboratory Contact PD (ex-China):** Syneos Health Karlin Karlmark, Manager Les Templiers 2400 route des Colles 06410 Biot, Sophia-Antipolis FRANCE Phone: +33 (0) 171 162 386 Email: karlin.karlmark@syneoshealth.com
Laboratory Contact China: Eurofins Central Laboratory Jane Zhu, Site Manager F7, 395 West Jiangchang Road Shanghai, P.R. China 200436 Phone number: +86 21 6181 7503 Fax number: +86 21 6181 7501 E-mail: janezhu@eurofins.com	**Laboratory Contact PK and PD (China):** Frontage Laboratories (Shanghai) Co. Ltd. Xuanyi Zhou, Manager No. 67-13, Libing Road, Pudong New District Shanghai, P.R. China 201203 Direct: +86 (0)21-50796268, Ext: 779 Mobile: +86 18217009357 Email: xuanyizhou@frontagelab.com.cn

TABLE OF CONTENTS

LIST OF TABLES

PROTOCOL SYNOPSIS

Protocol Title	A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate CBP-201 in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps
Investigational Product	CBP-201 for subcutaneous injection
Reference Product	Placebo
Indication	Chronic Rhinosinusitis with Nasal Polyps
Protocol Number	CBP-201-WW003
Study Phase	Phase 2
Number of Study Sites	Multiple study sites (approximately 70 sites), in the United States, China, European Union and Eurasian Economic Union
Number of Patients Planned	147
Objectives	**Primary Objectives:** To evaluate the efficacy of CBP-201 on a background of mometasone furoate nasal spray (MFNS) in reducing endoscopic nasal polyp score (NPS) and nasal congestion/obstruction score (NCS) severity in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) whose disease remains inadequately controlled despite daily treatment with intranasal corticosteroid (INCS) therapy in comparison to placebo. **Secondary Objectives:** To evaluate the effect of CBP-201 on: • Symptoms of sinusitis • Computed tomography image scores of nasal polyps and sinus inflammation • Patient reported outcomes (PROs) and health-related quality of life (HRQoL) • Safety and tolerability of CBP-201 in patients with CRSwNP **Exploratory Objectives:** • To evaluate the effect of CBP-201 in the subgroups of patients with comorbid asthma • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CBP-201 in patients with CRSwNP
Study Design	Multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of CBP-201 in patients with CRSwNP whose disease remains inadequately controlled despite daily treatment with INCS therapy. The study consists of 3 periods: **Screening/Run-in Period: (Up to 31 days)** Beginning at the first screening visit and throughout the duration of the treatment period, patients will be asked to standardize their INCS to a regimen of mometasone furoate (NASONEX®) nasal spray (MFNS) of 2 actuations (50 mcg/actuation) in each nostril twice daily (BID), total daily dose of up to 400 mcg, unless they are intolerant to BID INCS in which case, they may remain on a stable dosage of mometasone of 2 actuations (50 mcg /actuation) in each nostril once daily, total daily dosage of 200 mcg. The screening period can be up to 31 days to allow for a run-in of at least 28 days if the

	patients have not been on a documented steady dose of INCS prior to screening. If the patients are able to document steady use, then the run-in period may be shortened to as little as 7 days (with patient diary entry to confirm compliance). **Treatment Period: (CBP-201/placebo for 24 weeks)** After screening/run-in has been completed, eligible patients will be randomly allocated in a 1:1:1 ratio to receive double-blind treatment with CBP-201 or placebo with every other week visits to the study site for subcutaneous (SC) injections: • CBP-201 300 mg every 2 weeks SC administration for 24 weeks with an initial loading dose of 600 mg at Day 1 • CBP-201 300 mg every 4 weeks SC administration for 24 weeks with an initial loading dose of 600 mg at Day 1. These patients will also receive volume matched placebo every 4 weeks on alternating visits to maintain the study blind. • Placebo every 2 weeks SC administration for 24 weeks (Placebo loading at Day 1) Randomization will be stratified by comorbid asthma. All patients will continue stable dose of MFNS (200 mcg) BID or once daily used during run-in period throughout the study. **Post-treatment Follow-up Period: (8 weeks)** After completing 24 weeks of treatment with the investigational product (IP) (or following early discontinuation of IP), patients will be followed for additional 8 weeks. Patients will be asked to complete a study visit every 4 weeks for follow-up assessments.
Main Eligibility Criteria:	**Inclusion Criteria** A patient must meet the following criteria to be eligible to participate in this study: 1. Female and male patients aged $\geq$ 18 and $\leq$ 75 years at the time of screening. 2. Patients who are diagnosed with chronic rhinosinusitis with bilateral polyps despite treatment with systemic corticosteroid within the past 2 years and/or medical contraindication/intolerance to systemic corticosteroids. The polyps have a minimum bilateral NPS of 5 out of a maximum score of 8 with at least a score of 2 for each nostril at screening (central read) and baseline (local read) evaluated by endoscopy. *Note: Patient intolerance to systemic corticosteroids includes patient refusal of treatment with systemic corticosteroids due to undesirable side effects.* 3. Nasal congestion/blockade/obstruction with moderate or severe symptom severity (Nasal Congestion Score of $\geq$ 2) at screening and a weekly average severity of > 1 at time of randomization. 4. Patients using a documented stable dose of nasal mometasone at least 200 mcg/day, or an equivalent daily dose of another INCS, for at least 28 days before randomization and willing to continue the dose for the duration of the study. *Note: For patients who are using an INCS product other than MFNS prior to the screening visit, the investigator must switch the patient to MFNS at V1. Patients must use nasal mometasone at least 200 mcg/day, or equivalent, for at least 28 days before randomization, which can include 21 days prior to screening with supportive documentation. Run-in can be 7-31 days with the compliance determined in the week prior to dosing.* 5. Patients willing to enter patient diary daily symptom assessments and maintain stable dosing with MFNS with a compliance of at least 70% in the 7 days preceding randomization. *Note: 70% compliance will be calculated as at least 5 of*

7 DAYS of MFNS use in the 7 days prior to randomization AND at least 5 of 7 DAYS of NCS completion in the patient diary in the 7 days prior to randomization.

6. Male patients who are non-sterilized and sexually active with a female partner of childbearing potential agree to use highly effective contraception from randomization until 8 weeks after last dose.
7. Female patients of childbearing potential who are sexually active with a nonsterilized male partner should have a confirmed negative serum beta-human chorionic gonadotropin test at Visit 1 and agrees to use highly effective contraception from signing of informed consent throughout the duration of the study and for 8 weeks after last dose.
8. Patient is able to understand and willing to sign the informed consent form (ICF) prior to any study related procedures being performed.
9. Willing and able to comply with all study visits and study-related procedures, in the opinion of the Investigator.

Exclusion Criteria

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

10. Patients unable to use MFNS.
11. Patients who are taking or have taken the following prohibited therapies as specified:
    a. Systemic steroids within 28 days prior to screening,
    b. Other nonbiologic investigational drugs within 60 days (or 5 half-lives, whichever is longer) of screening,
    c. Intranasal corticosteroid drops or corticosteroid-administering devices (eg, OptiNose device or stents) within 28 days prior to screening,
    d. Non-steroidal immunosuppressants (eg, cyclosporine, methotrexate, azathioprine, mycophenolate, sirolimus, tacrolimus) within 60 days or 5 half-lives, whichever is longer, of screening,
    e. Any monoclonal antibody therapy (eg, benralizumab, mepolizumab, omalizumab, resilizumab, dupilumab) or investigational biologic drug for asthma or other diseases within 60 days or 5 half-lives, whichever is longer, of screening,
    f. Leukotriene antagonists/modifiers within 7 days prior to screening for patients who were not on continuous treatment for ≥ 30 days prior to screening,
    g. Allergen immunotherapy for patients who were not on maintenance treatment for at least 90 days prior to screening,
    h. Any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate) within 30 days or 5 half-lives (whichever is longer) prior to screening.
    i. Any investigational small molecule drug or treatment within 16 weeks or 5 half-lives (whichever is longer) prior to screening.
12. Patients who did not respond favorably to previous dupilumab treatment (eg, therapy failure or patient experienced an adverse reaction to treatment).
13. Patients who have undergone any nasal surgery (including polypectomy) within 6 months before screening; or have a history of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS is not possible or have had uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing.

	14. Patients with conditions/concomitant diseases making them non evaluable at screening or for the primary efficacy endpoint such as: antrochoanal polyps, nasal septal deviation that would occlude at least 1 nostril, acute sinusitis, nasal infection or upper respiratory infection at screening or within 2 weeks before screening, ongoing rhinitis medicamentosa; known or suspected diagnosis of cystic fibrosis; chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (Wegener's Granulomatosis), eosinophilic granulomatous with polyangiitis (Churg-Strauss syndrome), Young's syndrome, primary dyskinetic ciliary syndromes (eg, Kartagener's syndrome) or other dyskinetic ciliary syndromes. 15. Signs or a CT scan suggestive of Allergic Fungal Rhinosinusitis 16. Patients with co-morbid asthma are excluded if: a. Forced Expiratory Volume in 1 second (FEV_1) ≤ 50% of normal predicted value OR b. An exacerbation within 90 days prior screening that required hospitalization (> 24 hours) OR c. Are on a daily dose of inhaled corticosteroids (ICS) higher than 1000 mcg fluticasone propionate or the equivalent. 17. Known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, human immunodeficiency virus (HIV), listeriosis, pneumocystosis, or tuberculosis, despite infection resolution; or unusually frequent, recurrent or prolonged infections. Tuberculosis testing would be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees. 18. Patients who have active Hepatitis B, Hepatitis C or HIV infections as determined by positive results at Screening for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb); or hepatitis C virus antibody (HCVAb); or positive HIV serology. *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.* 19. A helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent that has not been treated, or has failed to respond to, standard of care therapy. 20. Evidence of infection requiring treatment with systemic antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 7 days before baseline, or viral infections within 14 days before screening that may not have received antiviral treatment. 21. Live, attenuated vaccinations within 28 days prior to screening or planned live, attenuated vaccinations during the study. 22. Pregnant or intent to become pregnant during the study, or breast-feeding women. 23. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the

	opinion of the investigator and may affect the safety of the patient throughout the study, or influence the findings of the studies or their interpretations, or impede the patient's ability to complete the entire duration of study. 24. Any clinically significant abnormal findings in physical examination, vital signs, safety lab tests during screening/run-in period, which in the opinion of the investigator, may put the patient at risk because of their participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study. 25. Have any of the following laboratory abnormalities at Screening: a. Eosinophils >1500 cells/mm^3 (or 1.5 x 10^9/L) b. Platelets <100000 cells/mm^3 (or 100 x 10^9/L) c. Creatine phosphokinase (CPK) > 10 upper limit of normal (ULN) d. Alanine aminotransferase (ALT) > 2.5 times the ULN e. Aspartate aminotransferase (AST) ≥ 2.5 times the ULN f. Bilirubin ≥ 2 times the ULN 26. History of alcohol or drug abuse within 12 months prior to the date informed consent. 27. 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. 28. Plans to undergo any surgical procedure requiring general anesthesia during the study. 29. History of cancer: Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent. *Note: Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date of informed consent.*
Study Duration	Approximately 36 weeks including screening period up to 4 weeks, 24-week treatment period, and 8-week period of additional follow-up.
Test Products and Route of Administration	CBP-201: provided as a single-use 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution of CBP-201 targeted to be approximately 150 mg/mL. Placebo: provided as a single-use 2 mL vial containing 1.2 mL solution containing identical excipients without CBP-201. Matched volumes and number of vials are to be used for placebo doses. Study drug will be administered by SC injection.
Dose Regimen	Randomized 1:1:1 to the following double blinded treatment: • CBP-201 300 mg SC every 2 weeks with a 600 mg loading dose on Day 1 • CBP-201 300 mg SC every 4 weeks with 600 mg loading dose on Day 1. This group will also receive matched placebo every 4 weeks on alternate weeks to maintain the blind • Placebo SC every 2 weeks with matched volume placebo loading dose on Day 1
Study Endpoints	
Efficacy	**Primary Efficacy Endpoints:**

	There will be 2 co-primary endpoints: • Change from baseline at Week 24 in endoscopic NPS Endoscopic NPS is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0 to 8; higher scores indicate worse status). • Change from baseline at Week 24 in average daily nasal congestion score (NCS) **Secondary Efficacy Endpoints:** • Change from baseline at Week 24 in: – Percentage of maxillary sinus volume occupied by disease on CT and Lund-Mackay Computed Tomography scores from patients enrolled at Study Sites that are approved and qualified to perform CT scans – University of Pennsylvania Smell Identification Test (UPSIT) – Visual analogue scale for rhinosinusitis (VAS-RS) – Total nasal symptom score (TNSS) – 22-item Sinonasal Outcome Test (SNOT-22) – Average daily anterior rhinorrhea score – Average daily posterior rhinorrhea score – Average daily loss of smell score – Daily subject-assessed nasal peak inspiratory flow (NPIF) • Requirement of rescue treatment (systemic CS for > 5 consecutive days) or having had surgery for nasal polyps through Week 24 • Time to rescue treatment (systemic CS for > 5 consecutive days) or surgery for nasal polyps through Week 24. **Exploratory endpoints:** • Change from baseline at Week 24 in FEV_1 for subjects with asthma • Proportion of patients with minimal clinically important difference $\geq$ 8.9 in SNOT-22 at Week 24 • Change from baseline at Week 16 in endoscopic NPS • Change from baseline at Week 16 in Average daily NCS • Change from baseline at Week 24 in European quality of life scale (EQ-5D-5L) • Healthcare resource utilization through Week 24
Safety	**Safety and Tolerability:** Safety endpoints will be summarized by descriptive statistics and narratives where indicated by severity. • Adverse events (AEs) reported, including SAEs and adverse events of special interest (AESI) • Vital signs • Physical examination • Electrocardiogram (ECG) parameters • Injection site evaluations

	• Safety laboratory parameters • Antidrug antibodies (ADA) and neutralizing antibodies (NAb)
Pharmacokinetics	Whole blood for plasma CBP-201 concentrations will be obtained and analysed. The individual and mean steady-state trough PK profile will be calculated and additional PK parameters may be estimated from a population PK model. Additional sampling will be obtained after the last treatment dose as noted above to characterize the return to baseline.
Pharmacodynamics	Change from baseline in Biomarkers in the blood [including total immunoglobulin E (IgE), eosinophil count, eosinophil cationic protein, thymus and activation regulated chemokine (TARC), Eotaxin-3, and periostin].
Statistical Considerations:	Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate Statistical Analysis Plan. **Analysis Populations** Five populations will be defined: Randomised Set (RS), Full Analysis Set (FAS), Per Protocol Set (PPS), Safety Set (SS), and PK Set (PKS). The primary analyses of all efficacy endpoints will be conducted in the Full Analysis Set (FAS). Supportive efficacy analyses will be conducted in the Per Protocol Set (PPS). **Primary Efficacy Analysis** The co-primary endpoints (change from baseline in NPS and average daily NCS at Week 24) will be analysed using SAS proc MIXED procedure in the Full Analysis Set. Statistical comparisons between each treatment group and placebo will be performed. **NPS**. The linear mixed model will be applied to change from baseline to each timepoint through Week 24 in endoscopic NPS to evaluate the treatment effect of the primary endpoints. The fixed effects will be included as followed: treatment group, endoscopic NPS at baseline, visit, interaction between treatment group and visit, and the presence of comorbid asthma in the model. Patient will be included as a random effect. Based on the model, t-test will be performed for least square means of interaction between treatment group and visit of Week 24, with two-sided significance level of 0.05. 95% confidence interval for least square means of interaction between treatment group and visit of Week 24 will be calculated. Covariance matrix applied to the within-subject error will be estimated by Restricted maximum likelihood (REML). The Kenward-Roger approximation will be used to estimate the degree of freedom. Details of assumption on variance structure will be described in the SAP. **Average daily NCS**. A similar model used for NPS will be performed for the average daily congestion score (NCS). **Sample Size Estimation** The sample size estimation is based on the comparison between CBP-201 300 mg every 2 weeks vs. placebo with regard to the co-primary endpoint of NPS: change from baseline in NPS at Week 24. Assuming a common standard deviation in the NPS of 2.1, and based on the use of a two-sided test at the alpha=0.05 level , 41 patients per group will provide 80% power to detect a difference of 1.3 between the CBP-201 group and the placebo group in the change of NPS from baseline to Week 24. To allow for a 15% dropout rate, the planned sample size is 49 subjects per group (147 total).

Table 1: Schedule of Assessments

Assessments	Screen	Base-line	Treatment Period													Follow-up Period		Unsched-uled Visits[t]	Early Termina-tion (+7d)
	D-31 to D-1[a]	D1	D8 W1 (±3d)	D15 W2 (±3d)	D29 W4 (±3d)	D43 W6 (±3d)	D57 W8 (±3d)	D71 W10 (±3d)	D85 W12 (±3d)	D99 W14 (±3d)	D113 W16 (±3d)	D127 W18 (±3d)	D141 W20 (±3d)	D155 W22 (±3d)	EOT D169 W24 (±3d)	D197 W28 (±5d)	EOS D225 W32 (±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																	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																		
Body Weight	X	X							X						X		X		X
Complete Physical Examination[c]	X																X		X
Brief Physical Examination[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
CT scan[u]	X														X				X
NCS[e]	X	X	X	X	X		X		X		X		X		X		X	X	X
EQ-5D-5L		X			X				X						X		X	X	X
VAS-RS	X	X	X	X	X		X		X		X		X		X		X	X	X
SNOT-22	X	X	X	X	X		X		X		X		X		X		X	X	X
TNSS	X	X	X	X	X		X		X		X		X		X		X	X	X
Nasal endoscopy NPS	X	X[f]		X			X				X				X		X		X
Spirometry[g]	X	X			X		X		X						X		X	X	X

Assessments	Screen	Base-line	Treatment Period													Follow-up Period		Unsched-uled Visits[t]	Early Termina-tion (+7d)
	D-31 to D-1[a]	D1	D8 W1 (±3d)	D15 W2 (±3d)	D29 W4 (±3d)	D43 W6 (±3d)	D57 W8 (±3d)	D71 W10 (±3d)	D85 W12 (±3d)	D99 W14 (±3d)	D113 W16 (±3d)	D127 W18 (±3d)	D141 W20 (±3d)	D155 W22 (±3d)	EOT D169 W24 (±3d)	D197 W28 (±5d)	EOS D225 W32 (±5d)		
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	NA	NA
Smell test (UPSIT)		X	X	X	X				X						X		X	X	X
12-Lead ECG	X	X							X						X		X		X
Hepatitis & HIV Screens[h]	X																		
Pregnancy Test[i]	X	X			X		X		X		X		X		X	X	X		X
Dispense or Review Patient Diary/ NPIF Meter[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization		X																	
Health Care Resource Utilization[k]		X			X		X		X		X		X		X		X		X
Urinalysis	X	X							X						X		X		X
Serum Chemistry[l]	X	X	X		X		X		X		X		X		X	X	X		X
Hematology[m]	X	X	X		X		X		X		X		X		X	X	X		X
PK Blood Sample[n]		X	X		X				X						X	X	X		X
PD Blood Sample[o]		X	X		X				X						X		X		X
Blood Sample for ADA, Nab[p]		X			X				X						X		X		X
Study Drug SC Administration[q]		X		X	X	X	X	X	X	X	X	X	X	X	X				
Dispense rescue medication and MFNS as needed[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess Injection Site(s)[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibodies; AE = adverse event; CT = computed tomography; D = Day, ECG = electrocardiogram; EOS = End-of-Study; EOT = End-of-Treatment; EQ-5D-5L = European quality of life questionnaire; FEV_1 = forced expiratory volume in the first second of expiration; HBcAb = hepatitis B core antibody; HCVAb = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; LABA = long-acting ß-agonist; NAb = neutralizing antibody; NCS = Nasal Congestion Score; NPS = Nasal Polyp Score; NPIF = Nasal peak inspiratory flow; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SABA = short-acting ß-agonists; SC = subcutaneous; SNOT-22 = 22-item Sinonasal Outcome Test; TNSS = Total Nasal Symptom Score; UPSIT = University of Pennsylvania Smell Identification Test; V = visit; VAS-RS = Visual Analogue Scale for Rhinosinusitis; VS = vital signs; W = Week.

Footnotes:

a. The screening period to collect baseline data and determine a patient's eligibility is 31 days in duration and begins when the ICF is signed.
b. Vital signs include body temperature, respiratory rate, blood pressure, and heart rate. VS should be recorded predose for all treatment visits. On D1 (V2), W2 (V4), and W4 (V5), VS should be recorded hourly during the 2hour postdose monitoring period. On W6 (V6) and beyond, VS should be recorded at 30 minutes postdose. During the post-treatment Follow-Up Period, VS are to be recorded once during each visit. Vital signs may be modified if adapted to telemedicine or home health visits where continuous monitoring may not be possible.
c. A complete physical examination will be performed, which assesses the following: general appearance, skin, eyes/ears/nose/throat, thyroid, head and neck, cardiovascular system, respiratory system, abdomen, fundoscopy (optional), extremities, lymph nodes, musculoskeletal, and nervous system.
d. A brief physical examination will include an assessment of general appearance, eyes, lungs, and lymph nodes. Physical exams may be modified if adapted to telemedicine or home health visits.
e. The Nasal Congestion Score should be captured in the patient diary but may be captured by an alternative manner (ie, paper) if the device fails between clinic visits.
f. If V2 is performed within 7 days of V1, the NPS (central read) from V1 will be used to confirm eligibility, and the endoscopy will not be repeated at V2. For more details see section 7.8.1 Endoscopic Nasal Polyp Score.
g. Spirometry, including FEV_1, forced vital capacity, and peak expiratory flow, will be performed only for patients with asthma. Due to diurnal variation of lung function, it is important that all spirometry assessments are performed preferably after 7:00 hours and no later than 11:00 hours. Prior to spirometry assessments, twice-daily LABA therapies, including combination therapies, should be withheld ≥12 hours, once-daily therapies containing LABA or long-acting muscarinic antagonists should be withheld for ≥ 24 hours, and SABAs should be withheld ≥6 hours. Reversibility of lung function will be tested if a medical history record of ≥12% reversibility (improvement in FEV_1) cannot be demonstrated within the previous 12 months.
h. Hepatitis screen: For more details see section 7.6.
i. All women of childbearing potential 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.
j. A patient diary and NPIF meter will be issued to the patient with training at Screening visit. At all study visits, patients should be assessed for compliance and re-trained, if necessary, on the use of the patient diary device and NPIF meter.
k. A questionnaire of Health Care Resource Utilization will be administered. For more details see section 7.8.12.
l. Serum chemistry panel: sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, glucose, calcium, uric acid, total protein, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyltransferase, creatine phosphokinase, total cholesterol, triglycerides, and C-reactive protein. 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.
m. Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count with 5-part differential count, differential count, and total red blood cell count.
n. PK blood samples should be collected prior to dosing; date and clock time for each sample should be recorded.
o. PD blood samples for biomarkers of inflammation include Eotaxin-3, eosinophil cationic protein, total immunoglobulin E, thymus and activation-regulated chemokine, and periostin. Blood eosinophil count will be measured as part of hematology test. C-reactive protein will be determined as part of the serum chemistry.
p. ADA blood sample: NAb will be tested at all ADA collection time points in samples that are ADA positive.

q. Patients are to be observed 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 noted otherwise. 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 in the same anatomical location used during the previous visit.

r. Dispense albuterol/salbutamol MDI for reversibility testing and as an optional take-home rescue medication for those patients with asthma. Patients should be offered replacements as needed for symptom control throughout the study and should be reminded to document the use in their patient diary. Sites may also provide MFNS for required concomitant use as needed.

s. 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. On all dosing days, the new injection site should be assessed prior to the patient's release. The 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 AE. See section 8.6 for more details.

t. Unscheduled visits may be conducted as needed, and additional assessments performed at these visits are at the discretion of the Investigator.

u. CT scan will only be required for subjects that are enrolled at Study Sites that are approved and qualified to perform CT Scans.

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
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
BID	twice daily
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRO	contract research organization
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	corticosteroid
CV	curriculum vitae
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
PRO	patient-reported outcomes
ERS	European Respiratory Society
EQ-5D-5L	EuroQol Health Status Measure, 5 Dimensions/5 Levels
EQ-VAS	EQ visual analogue scale
EU	European Union
FAS	Full Analysis Set

ABBREVIATION	TERM
FDA	Food and Drug Administration (US)
FEV_1	forced expiratory volume in the first second of expiration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
ICF	informed consent form
ICS	inhaled corticosteroid(s)
IgE	immunoglobulin E
IL	interleukin (IL-4, IL-13, etc)
INCS	intranasal corticosteroid
IND	investigational new drug
IP	investigational product
IRB	Institutional Review Board
LABA	long-acting ß agonist
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered Dose Inhaler
MFNS	mometasone furoate nasal spray
NAb	neutralizing antibody
NCS	nasal congestion/obstruction score
NPIF	nasal peak inspiratory flow
NPS	nasal polyp score
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

ABBREVIATION	TERM
PKS	PK set
PPS	Per Protocol Set
PROs	patient reported outcomes
QTcF	QT interval corrected for heart rate using Fridericia's formula
RS	Randomised Set
SABA	short-acting ß agonist
SAE	serious adverse event
SC	subcutaneous
SS	safety set
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation-regulated chemokine
TEAE	treatment-emergent adverse event
TNSS	total nasal symptom score
ULN	upper limit(s) of normal
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VAS-RS	visual analogue scale for rhinosinusitis
VS	vital signs
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Background

Chronic rhinosinusitis with or without nasal polyps has a high prevalence and significantly affects health-related quality of life in affected patients (Avdeeva 2018). Chronic rhinosinusitis, an inflammation of the nose and paranasal sinuses, is delineated by 2 or more symptoms: blockage or nasal discharge and/or facial pain/pressure and/or loss of smell (Fokkens 2020). This condition affects 11 to 12% of the population in various geographic locations (Hastan 2011; Kim 2016; Hirsch 2017). Phenotypes of chronic rhinosinusitis initially are divided by the presence or absence of polyps based on endoscopic examination or radiologic imaging (Fokkens 2020).

Endotyping of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) has increased and has some benefit for treatment selection (Cardell 2020). New treatment options are now being explored based on the finding that type 2 immune reactions occur in greater than 80% of nasal polyp cases in Europe and the United States (US) (Cardell 2020). Current treatment explorations target anti-immunoglobulin E (IgE) pathways, anti-interleukin (IL-5) mechanisms, and anti-IL-4 and IL-13 receptor mechanisms (Avdeeva 2018). A study testing subcutaneous (SC) dupilumab, a human monoclonal antibody that blocks the IL-4Rα subunit in type 2 inflammation, demonstrated a positive outcome of the drug on nasal polyp score (NPS), a SinoNasal Outcome Test, and an improved sense of smell in patients with CRSwNP who were unresponsive to topical corticosteroids (CS) (Bachert 2016).

1.2 Investigational Product

CBP-201 is a novel human monoclonal antibody directed against the cell surface protein IL-4Rα. It is an Investigational Medicinal Product 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-4Rα, Dupixent® (dupilumab) (Dupixent® 2019), the CBP-201 clinical development program 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 US, Australia, New Zealand, China, and the European Union (EU) has recently completed dosing and is in the reporting phase. A Phase 2 study in patients with asthma is on-going in

the US with additional planned sites in China and the EU, Ukraine and South Korea. 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 treatment-emergent adverse events (TEAEs) to date have been mild to moderate in severity. No clinically relevant trends in clinical safety laboratory data or vital sign data have been observed 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, International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and applicable regulatory requirements.

2 STUDY OBJECTIVES

2.1 Primary Study Objective

To evaluate the efficacy of CBP-201 on a background of mometasone furoate nasal spray (MFNS) in reducing endoscopic NPS and nasal congestion/obstruction score (NCS) severity in patients with CRSwNP whose disease remains inadequately controlled despite daily treatment with intranasal corticosteroid (INCS) therapy in comparison to placebo.

2.2 Secondary Objectives

To evaluate the effect of CBP-201 on:

- Symptoms of sinusitis
- Computed tomography image scores of nasal polyps and sinus inflammation
- Patient reported outcomes (PROs) and health-related quality of life (HRQoL)
- Safety and tolerability of CBP-201 in patients with CRSwNP

2.3 Exploratory Objectives

- To evaluate the effect of CBP-201 in the subgroups of patients with comorbid asthma
- To evaluate the PK and PD of CBP-201 in patients with CRSwNP

3 INVESTIGATIONAL STUDY PLAN

3.1 Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of CBP-201 in patients with CRSwNP whose disease remains inadequately controlled despite daily treatment with INCS therapy.

The study consists of 3 periods:

3.2 Screening/Run-In Period: 4 weeks

The Screening Period is 31 days. Patients using a documented stable dose of nasal mometasone at least 200 mcg/day, or an equivalent daily dose of another INCS, for at least 28 days before randomization will be asked to continue the dose for the duration of the study. For patients who are using an alternative INCS product other than MFNS prior to the screening visit, the investigator must switch the patient to MFNS at Visit 1. Patients will be asked to standardize their INCS to a regimen of mometasone furoate (NASONEX®) nasal spray (MFNS) of 2 actuations (50 mcg/actuation) in each nostril BID, total daily dose of up to 400 mcg, unless they are intolerant to BID INCS, in which case, they may remain on a stable dosage of mometasone of 2 actuations (50 mcg /actuation) in each nostril once daily, total daily dosage of 200 mcg.

Patients must use nasal mometasone at least 200 mcg/day, or equivalent, for at least 28 days before randomization, which can include days prior to screening with supportive documentation. Run-in can be 7-31 days with compliance determined in the week prior to randomisation using patient diary entries. If patients fail compliance requirements, they may undergo retraining with the patient diary and repeat the run-in period of 7 days.

3.3 Treatment Period: CBP-201/Placebo for 24 weeks

After screening/run-in has been completed, eligible patients will be randomly allocated in a 1:1:1 ratio to receive double-blind treatment with CBP-201 Q2W or Q4W or placebo with every other week visits to the study site for SC injections:

- CBP-201 300 mg every 2 weeks SC administration for 24 weeks with an initial loading dose of 600 mg at Day 1
- CBP-201 300 mg every 4 weeks SC administration for 24 weeks with an initial loading dose of 600 mg at Day 1. This group will also receive matched placebo every 4 weeks on alternate weeks to maintain the blind.
- Placebo every 2 weeks SC administration for 24 weeks (Placebo loading at Day 1)

Randomization will be stratified by comorbid asthma.

During the double-blind randomized treatment, all patients will continue stable dose of MFNS (200 mcg) BID or once daily used during the run-in period.

3.4 Post-treatment Follow-Up Period: 8 weeks

After completing 24 weeks of treatment with the investigational product (IP) (or following early discontinuation of IP), patients will be followed for additional 8 weeks. Patients will be asked to complete a study visit every 4 weeks to:

- Evaluate PK, PD, antidrug antibodies (ADA), physical examination, QOL, efficacy, safety, and a last endoscopy at the end of study
- Continue to complete patient diary for symptom evaluation
- Continue MFNS stable dose during post-treatment period
- Report any AE

Patients will be encouraged to remain in the study even if discontinued from study drug treatment. Patients who discontinue prematurely from study drug treatment are assessed as soon as possible using the procedures normally planned for the End of Treatment Visit and the 2 post-treatment Follow-up Period Visits.

3.5 Discontinuation and Study Stopping Rules

Dosing for any individual patient will be stopped if the patient experiences a drug-related SAE or a drug-related significant nonserious adverse event (AE), 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 study drug treatment due to treatment failure.

3.6 Rationale for Study Design

CBP-201 simultaneously targets the inflammatory actions of both IL-4 and IL-13 of patients with inflammatory disease. This study is a standard add-on design for a Phase 2 trial in CRSwNP to assess both efficacy and safety of CBP-201. There will be a screening period of 31 days in which the patient's CRSwNP and health status will be assessed prior to dosing. At the Screening and Baseline Visits, the patient answers the symptoms questionnaires and will be assessed by endoscopy to measure the nasal polyp size prior to receiving study drug. If the patient fulfils the eligibility criteria, they will be randomized to 1 of 3 treatments: CBP-201 300 mg every 2 weeks, CBP-201 300 mg every 4 weeks or placebo every 2 weeks in a 1:1:1 treatment ratio. Patients will receive study drug or placebo every 2 weeks. Patients will be allowed to continue regular, protocol-permitted, concomitant medications. The patient's symptoms and nasal polyp size will be measured throughout the study with 2 co-primary endpoints being the change from baseline NPS and the NCS at Week 24 of treatment.

Patients will also be closely monitored throughout the study with patient diaries that will be conveying symptom and physiologic data to site staff for review. Patients will be regularly assessed by the physician at clinic, tele-visits, or home health care during the 24 weeks of treatment followed by an 8-week post-treatment follow-up period. As indicated in the Schedule of Assessment (Table 1), where possible, home health visits or telemedicine visits may be utilized to complete study visits when needed to adapt to COVID-19 pandemic restrictions and/or patient health concerns. Home healthcare and telemedicine may reduce the risk of missed visits due to study site closures and reduce the need for patients to visit the study site and therefore minimize the overall burden on patients.

3.7 Study Duration

The study duration is approximately 36 weeks including a Screening Period of up to 4 weeks, a 24-week Treatment Period, and an 8-week Post-treatment/Follow-up Period.

3.8 Study Population

It is anticipated that approximately 147 male and female patients with chronic rhinosinusitis with large bilateral nasal polyps that remain uncontrolled despite daily treatment with INCS will be recruited into the study.

Approximately 50% of the patients will be targeted to have comorbid asthma and treatment will be stratified on comorbid asthma. *Note: This may be demonstrated with a documented medical history of ≥12% reversibility (improvement in FEV_1) within the previous 12 months or may be demonstrated at screening in the clinic. Patients may repeat the reversibility on a different day if it is determined that a longer bronchodilator washout period is needed.*

3.9 Efficacy Assessments

3.9.1 Co-primary Efficacy Endpoints

There will be 2 co-primary endpoints:

- Change from baseline at Week 24 in endoscopic NPS
  - Endoscopic NPS is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0 to 8; higher scores indicate worse status)
- Change from baseline at Week 24 in average daily nasal congestion score (NCS)

3.9.2 Secondary Efficacy Endpoints

- Change from baseline at Week 24 in:

- Percentage of maxillary sinus volume occupied by disease on CT and Lund-Mackay Computed Tomography scores from patients enrolled at Study Sites that are approved and qualified to perform CT scans
- University of Pennsylvania Smell Identification Test (UPSIT)
- Visual analogue scale for rhinosinusitis (VAS-RS)
- Total nasal symptom score (TNSS)
- 22-item Sinonasal Outcome Test (SNOT-22)
- Average daily anterior rhinorrhea score
- Average daily posterior rhinorrhea score
- Average daily loss of smell score
- Daily subject-assessed nasal peak inspiratory flow (NPIF)

- Requirement of rescue treatment (systemic CS for > 5 consecutive days) or having had surgery for nasal polyps through Week 24
- Time to rescue treatment (systemic CS for > 5 consecutive days) or surgery for nasal polyps through Week 24

3.9.3 Exploratory Efficacy Endpoints

- Change from baseline at Week 24 in Forced Expiratory Volume in 1 Second (FEV_1) for patients with asthma
- Proportion of patients with minimal clinically important difference $\geq$ 8.9 in SNOT22 at Week 24
- Change from baseline at Week 16 in endoscopic NPS
- Change from baseline at Week 16 in NCS
- Change from baseline at Week 24 in European quality of life scale (EQ-5D-5L)
- Healthcare resource utilization through Week 24

3.9.4 Pharmacodynamic Endpoints

- Change from Baseline in blood levels of IgE
- Change from Baseline in peripheral eosinophil counts
- Change from Baseline in other markers of atopic inflammation in the blood [eosinophil cationic protein (ECP), thymus and activation-regulated chemokine (TARC), Eotaxin-3, and periostin.]

3.9.5 Pharmacokinetic Endpoints

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

Additional sampling will be obtained after the last treatment dose as noted above to characterize the return to baseline.

3.9.6 Safety Endpoints

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

- AEs reported, including SAEs and adverse events of special interest (AESI)
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Injection site evaluations
- Safety laboratory parameters evaluated
- ADA and neutralizing antibodies (NAb)

4 STUDY TREATMENTS

4.1 Study Drug Description

CBP-201: provided as a single-use 2 mL vial containing 1.2 mL clear to slightly yellow sterile solution of CBP-201 targeted to be approximately 150 mg/mL.

Placebo: provided as a single-use 2 mL vial containing 1.2 mL solution containing identical excipients without CBP-201. Similar volumes and number of vials are to be used for placebo doses.

4.2 Study Drug Administration

Eligible patients will receive study drug by SC injection and will randomized 1:1:1 to the following treatments:

- CBP-201 300 mg SC every 2 weeks with a 600-mg loading dose on Day 1
- CBP-201 300 mg SC every 4 weeks with a 600-mg loading dose on Day 1. This group will also receive volume matched placebo every 4 weeks on alternate visits to maintain the blind.
- Placebo volume-matched SC dosing every 2 weeks 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

As all patients will have significant rhinosinusitis and some patients will also have asthma, patients may be provided with rescue therapy options. In the case of worsening of endoscopic/radiologic signs and/or clinical symptoms requiring medical intervention, the Investigator may consider standard of care rescue treatment such as:

- Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection)
- Short course oral/systemic corticosteroids($\leq$ 5 consecutive days).
- Sino-nasal surgery for nasal polyps. Based on previous observations, at least 8 weeks of study drug treatment is recommended prior to resorting to surgery to allow an onset of the treatment effect. *Note: Patients receiving sino-nasal surgery during the study are required to discontinue study drug treatment as this is categorized as a treatment failure, although study assessments may continue.*

Rescue options are based on current standard of care, but Investigators are also referred to Scadding et al 2007 for in depth guidance for the management of rhinosinusitis and nasal polyposis.

In addition, in the case of worsening asthma symptoms, patients may be offered the following rescue therapies, or others as deemed appropriate by the investigator:

- Albuterol (also known as salbutamol, short-acting ß agonist [SABA] inhaler). *Note: Patients with asthma are allowed to use albuterol/salbutamol as needed and use will be documented daily via patient diary. 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.

Patients receiving rescue medication during the study should continue on study drug unless the Investigator decides to withdraw the study treatment. Before starting treatment with systemic corticosteroids, patients should come to the study site for clinical assessments including endoscopy and review of patient symptoms.

Patient scheduled for sino-nasal surgery may continue IMP up to the time of surgery or EOT whichever date comes first and at time of surgery will be permanently discontinued from study treatment and perform efficacy and safety assessments at the EOT visit and return to the site for additional visits as described in the Schedule of Assessment.

A patient may use a different SABA reliever other than that provided (eg, a different brand of albuterol/salbutamol). This information must be recorded in the daily patient 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.

4.4 Other Concomitant Medications

Patients will maintain regular treatment with INCS and should continue on a stable dose and schedule throughout the study and dose adjustment is not allowed.

Patients with comorbid asthma may also be currently taking inhaled corticosteroid (ICS) and should continue on a regular dose and schedule throughout the study. In the interests of the patients' safety and acceptable standards of medical care, the Investigator will be permitted to prescribe any treatment(s) at their discretion. All treatments, including prescription drugs, vitamins, or herbal medications taken within 28 days prior to 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

- Intranasal corticosteroid drops or CS-administering devices (eg, or OptiNose device or stents) are prohibited. Only mometasone furoate (NASONEX®) nasal spray (MFNS) or regional equivalent, if agreed with the medical monitor, will be permitted during the study as a nasal treatment.

- Patients may not use any marketed biologic drug (eg, omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab) within 60 days or 5 half-lives (whichever is longer) of screening and throughout the study.

- Non-steroidal immunosuppressants (eg, cyclosporine, methotrexate, azathioprine, mycophenolate, sirolimus, tacrolimus) are not permitted during the study.

- Leukotriene antagonists/modifiers for patients who were not on continuous treatment for ≥ 30 days prior to screening are prohibited taken within 7 days prior to screening. If the patients were on these medications for ≥30 days prior to screening they may continue on a stable dose and schedule.

- Patients may not initiate treatment with allergen immunotherapy from screening throughout the duration of the study; if they have been on maintenance allergen immunotherapy for at least 90 days prior to screening, they may stay on a stable dose of this therapy during the study and dose adjustment is not allowed.

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

- Patients may not use any investigational small molecule drug or treatment within 16 weeks or 5 half-lives (whichever is longer) prior to screening and throughout the study.

- From V1 and throughout the study, patients may not use locally administered nasal decongestants except for the purpose of study required nasal endoscopy.

4.6 Restrictions

If undergoing lung function testing, patients should be requested to:

- Refrain from SABA for at least 6 hours before Screening (Visit 1 and visits requiring lung function testing)

- Delay the morning dose of inhaled combination therapy or long-acting ß agonist (LABA) until after spirometry measurements at Screening (Visit 1) and visits requiring lung function testing. Twice-daily LABAs or combination products should be delayed for at least 12 hours and once-daily bronchodilators or combination products should be delayed for at least 24 hours.

Note: On the morning of the Screening visit, patients with asthma 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 before 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 screening test if they fail the initial attempt, provided there is reason to believe that the FEV_1 would improve during the time between tests. If patients forget to delay these medications during the dosing period, lung function measurement should be flagged in the eCRF with a note to document that a potentially confounding concomitant medication was taken prior to measurement.

4.7 Avoidance of Pregnancy

To include women of childbearing potential 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 highly effective contraception are:

1. Established use of oral, injected, transdermal or implanted hormonal methods of contraception.

2. Placement of an intrauterine device or intrauterine system

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. In countries where spermicide is not available or single barrier methods are not considered highly effective, a second, physical barrier method must be used.

4. Female sterilization (eg, 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 (eg, single sex monogamous relationships, committed absolute abstinence). *Note: Periodic abstinence (*eg, *calendar, ovulation, symptothermal, postovulation 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, bilateral 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 this time 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 who become pregnant while in the study must be immediately withdrawn from study drug 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 screen-failed and do not require further follow-up after the patient has been withdrawn from the study.

4.8 Measurement of Patient Compliance

All dosing is supervised in the clinic or by home health administration. 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 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 device. 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 PATIENT ENROLLMENT

5.1 Inclusion Criteria

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

1. Female and male patients aged ≥ 18 and ≤ 75 years at the time of screening.

2. Patients who are diagnosed with chronic rhinosinusitis with bilateral polyps despite treatment with systemic corticosteroid within the past 2 years and/or medical contraindication/intolerance to systemic corticosteroids. The polyps have a minimum bilateral NPS of 5 out of a maximum score of 8 with at least a score of 2 for each nostril at screening (central read) and baseline (local read) evaluated by endoscopy. *Note: Patient intolerance to systemic corticosteroids includes patient refusal of treatment with systemic corticosteroids due to undesirable side effects.*
3. Nasal congestion/blockade/obstruction with moderate or severe symptom severity (Nasal Congestion Score of ≥ 2) at screening and a weekly average severity of > 1 at time of randomization.

4. Patients using nasal mometasone at least 200 mcg per day, or equivalent daily dosing of another INCS, for at least 28 days before randomization, and willing to continue for the duration of the study. *Note: For patients who are using an alternative INCS product other than MFNS prior to the screening visit, the investigator must switch the patient to MFNS at V1. Patients must use nasal mometasone at least 200 mcg/day, or equivalent, for at least 28 days before randomization, which can include 21 days prior to screening with supportive*

documentation. Run-in can be 7-31 days with the compliance determined in the week prior to dosing

5. Patients willing to enter patient diary daily symptom assessments and maintain stable dosing with MFNS with a compliance of at least 70% in the 7 days preceding randomization. *Note: 70% compliance will be calculated as at least 5 of 7 DAYS of MFNS use in the 7 days prior to randomization AND at least 5 of 7 DAYS of NCS completion in the patient diary in the 7 days prior to randomization.*

6. Male patients who are nonsterilized and sexually active with a female partner of childbearing potential agree to use highly effective contraception from randomization until 8 weeks after last dose.

7. Female patients of childbearing potential who are sexually active with a nonsterilized male partner should have a confirmed negative serum beta-human chorionic gonadotropin test at Visit 1 and agrees to use highly effective contraception from signing of informed consent throughout the duration of the study and for 8 weeks after last dose.

8. Patient able to read and understand and willing to sign the informed consent form (ICF) prior to any study related procedures being performed.

9. Willing and able to comply with study visits and study-related procedures, in the opinion of the Investigator.

5.2 Exclusion Criteria

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

10. Patients unable to use MFNS.

11. Patients who are taking or have taken the following prohibited therapies as specified:

a. Systemic steroids within 28 days prior to screening

b. Other nonbiologic investigational drugs within 60 days (or 5 half-lives, whichever is longer) of screening,

c. Intranasal corticosteroid drops or CS-administering devices (eg, OptiNose device or stents) within 28 days prior to screening,

d. Non-steroidal immunosuppressants (eg, cyclosporine, methotrexate, azathioprine, mycophenolate, sirolimus, tacrolimus) within 60 days or 5 half-lives, whichever is longer, of screening,

e. Any monoclonal antibody therapy (eg, benralizumab, mepolizumab, omalizumab, resiluzumab, dupilumab) or investigational biologic drug for asthma or other diseases within 60 days or 5 half-lives, whichever is longer, of screening

f. Leukotriene antagonists/modifiers within 7 days prior to screening for patients who were not on continuous treatment for ≥ 30 days prior to screening

g. Allergen immunotherapy for patients who were not on maintenance treatment for at least 90 days prior to screening

h. Any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate) within 30 days or 5 half-lives (whichever is longer) prior to screening

i. Any investigational small molecule drug or treatment within 16 weeks or 5 half-lives (whichever is longer) prior to screening

12. Patients who did not respond favorably to previous dupilumab treatment (eg, therapy failure or patient experienced an adverse reaction to treatment).

13. Patients who have undergone any nasal surgery (including polypectomy) within 6 months before screening; or have a history of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS is not possible or have had uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing.

14. Patients with conditions/concomitant diseases making them non evaluable at screening or for the primary efficacy endpoint such as: antrochoanal polyps, nasal septal deviation that would occlude at least 1 nostril, acute sinusitis, nasal infection or upper respiratory infection at screening or within 2 weeks before screening, ongoing rhinitis medicamentosa; known or suspected diagnosis of cystic fibrosis; chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (Wegener's Granulomatosis), eosinophilic granulomatous with polyangiitis (Churg-Strauss syndrome), Young's syndrome, primary dyskinetic ciliary syndromes (eg, Kartagener's syndrome) or other dyskinetic ciliary syndromes.

15. Signs or a CT scan suggestive of Allergic Fungal Rhinosinusitis.

16. Patients with co-morbid asthma are excluded if:

    a. $FEV_1 \leq 50\%$ of normal predicted value.

    OR

b. An exacerbation within 90 days prior screening that required hospitalization (> 24 hours).

OR

c. Are on a daily dose of inhaled corticosteroids (ICS) higher than 1000 mcg fluticasone propionate or the equivalent.

17. Known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, human immunodeficiency virus (HIV), listeriosis, pneumocystosis, or tuberculosis, despite infection resolution; or unusually frequent, recurrent or prolonged infections. Tuberculosis testing would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethics committees.

18. Patients who have active Hepatitis B, Hepatitis C or HIV infections as determined by positive results at Screening for hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb) or hepatitis C virus antibody (HCVAb); or positive HIV serology. *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.*

19. 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

20. Evidence of infection requiring treatment with systemic antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 7 days before baseline, or significant viral infections within 14 days before screening that may not have received antiviral treatment.

21. Live, attenuated vaccinations within 28 days prior to screening or planned live, attenuated vaccinations during the study.

22. Pregnant or intent to become pregnant during the study, or breast-feeding women.

23. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and may affect the safety of the patient throughout the study, or influence the findings of the studies or their interpretations, or impede the patient's ability to complete the entire duration of study.

24. Any clinically significant abnormal findings in physical examination, vital signs, safety lab tests during screening/run-in period, which in the opinion of the investigator, may put the patient at risk because of their participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study

25. Have any of the following laboratory abnormalities at Screening:

    a. Eosinophils >1500 cells/mm^3 (or 1.5 x 10^9/L)

    b. Platelets <100000 cells/mm^3 (or 100 x 10^9/L)

    c. Creatine phosphokinase (CPK) > 10 upper limit of normal (ULN)

    d. Alanine aminotransferase (ALT) > 2.5 times the ULN

    e. Aspartate aminotransferase (AST) ≥ 2.5 times the ULN

    f. Bilirubin ≥ 2 times the ULN

26. History of alcohol or drug abuse within 12 months prior to the date of informed consent

27. 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

28. Plans to undergo any surgical procedures requiring general anesthesia during the study.

29. History of cancer: Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent. *Note: Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent.*

5.3 Randomisation 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 eligible for the double-blind phase of the study will be randomly assigned to receive 1 of 3 treatments: CBP-201 300 mg SC every 2 weeks, CBP-201 300 mg SC every 4 weeks or volume-matched placebo every 2 weeks.

Approximately 50% of the randomised patients will be targeted to have comorbid asthma, defined as ≥12% reversibility and use of ICS ≤1000ug/day. *Note: This may be demonstrated with a documented medical history of ≥12% reversibility (improvement in FEV_1) within the previous 12 months or may be demonstrated at screening in the clinic. Patients may repeat the reversibility on a different day if it is determined that a longer bronchodilator washout period is needed.*

At least 50% of the randomized patients will be targeted to have type 2 inflammation marked by baseline blood eosinophil count ≥ 300 cells/μL *As this is only a target, there will be no hard stop to recruitment but when the study begins to approach 35% patients with eosinophils <299 cells/μL, sites will be encouraged to identify more patients with ≥ 300 cells/μL.*

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. Allocation of each treatment will be balanced by the presence of comorbid asthma.

- Recruitment of NP patients without co-morbid asthma will stop when approximately 66 patients without asthma are randomized, and
- Patients with co-morbid asthma will continue to be randomized to complete a total number of 147 randomized NP patients.

Note: A screen-failed patient may be re-screened at the Investigator's discretion, at least 28 days after the original screening 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 person responsible for preparing and administering the randomization codes, the staff of the third-party vendor responsible for packaging study drug, the staff of third party vendors processing the PK samples and data, 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 and has completed unblinding.

Blinding, unblinding, and management of the randomisation codes will proceed according to an appropriate manual provided separately.

5.5 Reasons for Patient 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 study drug 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 withdrawal of the patient 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.

5.6 Rhinosinusitis or Asthma Exacerbation as Withdrawal Criterion

If there are safety concerns, the Investigator may, but is not required to, discontinue the patient's study drug treatment for lack of efficacy if the patient experiences a rhinosinusitis exacerbation that results in 1 or more of the following:

- Hospitalization due to rhinosinusitis

  OR

- Treatment with systemic steroids for > 5 days

  OR

- Decision to proceed to surgery for removal of nasal polyps.

The Investigator may, but is not required to, discontinue the patient's study drug treatment for lack of efficacy if the patient experiences an asthma exacerbation as defined as a deterioration of asthma that results in 1 of the following:

- Asthma requiring prolonged treatment increase of approximately 4 times the baseline dose of ICS or the physician-prescribed addition of additional controllers

  OR

- Hospitalization due to asthma

Even if the patient's study drug treatment is discontinued due to treatment failure, 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.

Note: Patients may experience symptoms of decreased asthma control that do not reach the level of the exacerbation criteria but warrant concern from the clinical site. These "loss of control events" are defined as follows: An increase of 6 or more reliever occasions (1 puff = reliever occasion) in a 24-hour period for ≥ 2 consecutive days along with decreased peak flow will fulfill the definition of "loss of asthma control." Loss of asthma control events should be flagged in the eCRF and may be further recorded as an AE (worsening of specific symptoms). Patients experiencing a loss of asthma control may remain in the study but the patient should be instructed to contact the site for management of symptoms.

5.7 Other Reasons as Withdrawal Criteria

The Investigator may also discontinue a patient's study drug 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.

Patients who develop any related grade 2 or higher cardiovascular, respiratory, or ophthalmic TEAE or any related grade 3 or higher TEAE involving other organ systems must be discontinued from further study drug treatment and monitored until resolution or stabilization.

5.8 Handling of Withdrawals

When a patient is withdrawn from study drug 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 from the study prior to randomization at Visit 2. If a patient withdraws or is withdrawn from the study prior to study drug treatment, this will be considered a screen failure and only the following information need be collected at their last visit: AEs, review of concomitant medications, return of patient diary, review of diary data.

It is vital to obtain follow-up data or continue visits for any patient withdrawn from study drug 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 drug treatment because of an AE, this event will be followed until resolution or stabilization.

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

5.9 Replacements

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

5.10 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 STUDY VISITS

Patients are requested to delay using bronchodilators prior to each visit where spirometry is performed (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 -31 to -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
- Record medical history and demographics
- Vital sign measurements
- Record height and body weight
- Review and record prior and concomitant medications
- CT Scan (only required for subjects that are enrolled at Study Sites that are approved and qualified to perform CT Scans)
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Nasal endoscopy and NPS scoring
- Spirometry (Baseline pulmonary function test) and reversibility testing if documentation of ≥12% reversibility is not available in the prior 12 months
- Complete physical examination
- 12-lead ECG
- Hepatitis & HIV Screens
- Pregnancy test (Blood collection for pregnancy test for female patients of childbearing potential at Visit 1 then urine pregnancy tests at subsequent visits)
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- Dispense and instruct eligible patients on the proper use of the handheld device to capture NPIF, patient diary of symptoms (rhinorrhea etc), concomitant medication use.
- Sites may also provide MFNS for required concomitant use
- Dispense optional take-home rescue medications (albuterol/salbutamol) to asthma patients, if needed. Instruct patients to document the use of albuterol/salbutamol in their patient diary.

- 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:

- Review patient diary and NPIF data; retrain patient on proper diary use, if necessary
- Review and record prior and concomitant medication
- Vital sign measurement
- Record weight
- NCS assessment
- EQ-5D-5L questionnaire
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Nasal endoscopy and NPS scoring
- Pulmonary function tests (Spirometry) for patients with comorbid asthma only
- Healthcare Resource Utilization Questionnaire
- Brief physical examination
- 12-lead ECG
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- PK blood sample (predose)
- ADA blood sample (predose)
- PD blood sample (predose)
- Verify eligibility.

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

- Review and record changes to concomitant medications
- Vital sign measurements
- Brief physical examination
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Hematology and serum chemistry tests
- PK blood sample (predose)
- PD blood sample (predose)
- Review patient diary and NPIF data
- Injection site assessment from the previous injection
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes to concomitant medications
- Vital sign measurements
- Brief physical examination
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Nasal endoscopy and NPS scoring
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes to concomitant medications
- Vital sign measurements
- Brief physical examination
- NCS assessment
- EQ-5D-5L Questionnaire
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Pulmonary function tests (Spirometry) for patients with comorbid asthma only
- Healthcare resource utilization questionnaire

- UPSIT assessment of smell
- Urine pregnancy test for female patients of childbearing potential
- Hematology and serum chemistry tests
- PK blood sample (predose)
- PD blood sample (predose)
- ADA blood sample (predose)
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications

- Vital sign measurements
- Brief physical examination
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Pulmonary function tests (Spirometry) for patients with comorbid asthma only
- Healthcare resource utilization questionnaire
- Nasal endoscopy and NPS scoring
- Urine pregnancy test for female patients of childbearing potential
- Hematology and serum chemistry tests
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Record body weight
- Brief physical examination
- NCS assessment
- EQ-5D-5L assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Pulmonary function test (Spirometry) for patients with comorbid asthma only
- UPSIT assessment of smell
- Healthcare resource utilization questionnaire
- 12-lead ECG
- Urine pregnancy test for female patients of childbearing potential
- Safety laboratory samples (hematology, serum chemistry, urinalysis)
- PK blood sample (predose)
- PD blood sample (predose)
- ADA blood sample (predose)
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Nasal endoscopy and NPS scoring
- Healthcare resource utilization questionnaire
- Urine pregnancy test for female patients of childbearing potential
- Hematology and serum chemistry tests
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment

- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Brief physical examination
- Vital sign measurements
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- NCS assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- Healthcare resource utilization questionnaire
- Urine pregnancy test for female patients of childbearing potential
- Hematology and serum chemistry tests

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

6.14 Visit 14 (Study Day 155 ± 3 days/Week22)

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

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical exam
- Review patient diary and NPIF data
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in of concomitant medications
- Vital sign measurements
- Brief physical exam
- Review of patient diary and NPIF data
- Record body weight
- CT scan (only required for subjects that are enrolled at Study Sites that are approved and qualified to perform CT Scans)
- NCS assessment

- EQ-5D-5L assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Nasal endoscopy and NPS scoring
- Pulmonary Function Tests (Spirometry) for patients with comorbid asthma only
- Healthcare resource utilization questionnaire
- 12-lead ECG
- Urine pregnancy test
- Safety laboratory samples (hematology, serum chemistry, urinalysis)
- PK blood sample (predose)
- PD blood sample (predose)
- ADA blood sample (predose)
- Administer study drug
- Injection site assessment
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Brief physical examination
- Review patient diary and NPIF data
- Hematology and serum chemistry tests
- PK sample

- Injection site assessment (previous injection)
- Urine pregnancy test
- Dispense optional take-home rescue medications (albuterol/salbutamol) to patients with asthma, if needed. Remind patients to document the use in their patient diary.
- 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:

- Review and record changes in concomitant medications
- Vital sign measurements
- Body weight recorded
- NCS assessment
- EQ-5D-5L assessment
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Nasal endoscopy and NPS scoring
- Pulmonary function tests (Spirometry) for patients with comorbid asthma only
- Healthcare resource utilization questionnaire
- Complete physical examination
- 12-lead ECG
- Urine pregnancy test
- Injection site assessment
- Safety laboratory samples (hematology, serum chemistry, urinalysis)
- PK blood sample
- PD blood sample

- ADA blood sample
- Collect the daily patient handheld device
- 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 and procedures should be completed in the order given below, if possible:

- Review and recording of changes in concomitant medications
- Vital sign measurements
- Body weight recorded
- CT scan (only required for subjects that are enrolled at Study Sites that are approved and qualified to perform CT Scans)
- NCS assessment
- EQ-5D-5L questionnaire
- VAS-rhinosinusitis assessment
- SNOT-22 assessment
- TNSS assessment
- UPSIT assessment of smell
- Nasal endoscopy and NPS scoring
- Pulmonary function tests (Spirometry) for patients with comorbid asthma only
- Healthcare resource utilization questionnaire
- Complete physical examination
- 12-lead ECG
- Urine pregnancy test
- Safety laboratory samples (hematology, serum chemistry, urinalysis)

- PK blood sample
- PD blood sample
- ADA blood sample
- Collect the daily patient handheld device
- AE review and recording

7 STUDY ASSESSMENTS

All study assessments must be performed by trained clinical study staff in clinic, or where possible, via tele-visits and/or home healthcare visits. For specific timepoints of each assessment, refer to the Schedule of Assessment (Table 1).

7.1 Demographic Data and Medical History

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

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 complete 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, abdomen, fundoscopy (optional), extremities, and nervous system.

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 complete physical examination is not required.

Physical exams may be modified if adapted to telemedicine or home health visits and any modifications will be noted in the eCRF.

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.

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 (End of Treatment), and 17 (End of Study) 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 timepoints indicated in the Schedule of Assessments (Table 1). The following parameters will be recorded:

- Rhythm
- Ventricular rate
- PR interval
- QRS duration
- QT
- QT interval corrected for heart rate using Fridericia's formula (QTcF)

The Investigator is 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 Study Sites. The Investigator should use the system-calculated ECG values for determining eligibility.*

7.6 Safety Laboratory Tests

Standard laboratory hematology, serum chemistry, urinalysis, and hepatitis B, hepatitis C and HIV screening will be processed and reported by a central laboratory (Eurofins) at various timepoints, per Schedule of Assessments (Table 1).

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, creatinine, uric acid, total bilirubin, sodium, potassium, calcium, chloride, bicarbonate, alkaline phosphatase (ALP), AST, ALT, lactate dehydrogenase, gamma-glutamyl transferase, CPK, albumin, total protein, total cholesterol, triglycerides, C-reactive protein, and glucose.

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

Hepatitis and HIV Screening: Hepatitis screen: HBsAg or HBcAb and hepatitis C virus antibody (HCVAb). A hepatitis C viral load test is to be carried out if HCVAb is positive. The patient should be excluded from the study in case of positive hepatitis C viral load test result. If the hepatitis C 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 interest 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 the results are abnormal and clinically significant.

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

The Investigator is responsible for reviewing and signing 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 timepoints specified in the Schedule of Assessments (Table 1). A serum pregnancy test will be performed at the Screening visit and a urine pregnancy test will be performed at all visits thereafter. A negative pregnancy test result must be obtained prior to randomization. Additional or more frequent pregnancy testing may be performed if required by local regulations.

7.8 Efficacy Assessments

7.8.1 Endoscopic Nasal Polyp Score

NPS is assessed by central video recordings of nasal endoscopy. The score (NPS) is the sum of left and right nostril scores, as evaluated by means of nasal endoscopy. NPS is graded based on polyp size as described in Table 2 and depicted in the NPS figures below.

Table 2: Endoscopic Nasal Polyp Score

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or large polyps medial to the middle turbinate (i.e., reaching below the middle turbinate).
4	Large polyps causing complete obstruction of the inferior nasal cavity (i.e., touching the floor of the nose).

Nasal Polyp Scoring Figures
MT – middle turbinate; IT – inferior turbinate

Figure 1 Nasal Polyp Score of 0

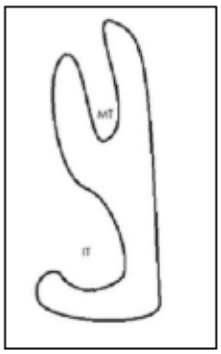


Figure 2 Nasal Polyp Score of 1

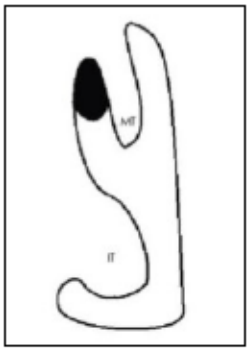


Figure 3 Nasal Polyp Score of 2

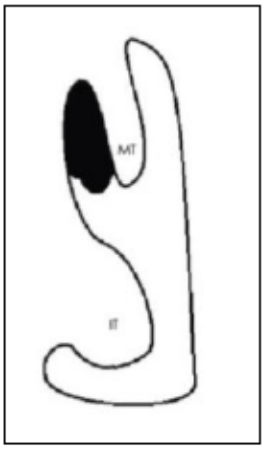


Figure 4 Nasal Polyp Score of 3

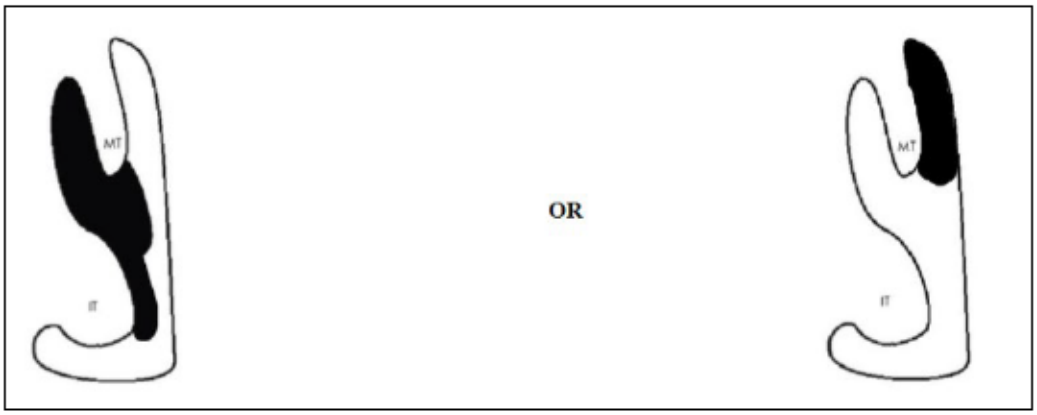
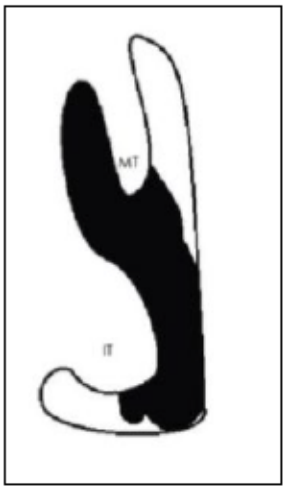


Figure 5 Nasal Polyp Score of 4



Note: Nasal endoscopy should be conducted at the end of the scheduled visits before the administration of study drug and preceded by local administration of anaesthetic drugs combined with a decongestant. Complete all assessments that might be affected by the procedure prior to application of the anaesthetic (i.e. UPSIT, SNOT-22, NCS, etc).

Standard video sequences will be available and sent to centralized reader. Centralized imaging data assessments and scoring by independent physician reviewer(s) for the imaging data will be performed for all endoscopies. At V1, the nasal endoscopy video must be sent for central reading and the results will be provided to the site. At Visit 2, if nasal endoscopy is performed (i.e. if V2 is >7 days after V1), the investigator will perform the nasal endoscopy and assess NPS to confirm eligibility. Thus, the patient's eligibility will be based on V1 central reading and, if performed, V2 local reading NPS score of ≥5 and ≥ 2 each side. The results of central reading from V2 onward will be available to sites after the study.

Central reading of V2 will be used for primary endpoint analysis to compare with the Week 24 readings. Further details on nasal endoscopy will be provided to sites in a separate operational manual.

If Baseline Visit (Visit 2) is performed within 7 days of Screening Visit (Visit 1) the NPS score (central read) from the screening visit will be used to confirm eligibility, and the endoscopy will not be repeated at Visit 2 unless there were technical difficulties with the Visit 1 scoring.

7.8.2 Daily Diary of Nasal Congestion / Obstruction Score

Daily NCS will be assessed by the patient through a patient diary from V1 throughout the study by using a 0 to 3 categorical scale for severity of symptoms from none to severe over the past 24 hours. This nasal congestion score is a co-primary endpoint and is very important to the outcome of the study and it is very important that the patients answer this question daily in the patient diary throughout the study including screening/run-in period.

How would you rate nasal congestion over the last 24 hours?

0 None

1 Minor

2 Moderate

3 Severe

7.8.3 Daily Diary of Other Symptoms

Patients will be required to keep a patient diary of rhinosinusitis and asthma symptoms BID. The purpose of the diary is to record the impact of their rhinosinusitis on daily activities, sense of smell, rhinorrhea, and medication use. The patients will also be required to perform NPIF testing at home and to record the results. 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 patient diary and discuss any concerns over symptom changes with the patient. Alarms will be programmed to encourage patients to contact the study staff if their symptoms worsen to indicate a possible exacerbation of their rhinosinusitis or asthma.

AM QUESTIONS:

1. **How many times did you awaken due to rhinosinusitis symptoms last night?**

   0 Did not awaken due to rhinosinusitis symptoms

   1 Awoke once due to rhinosinusitis symptoms

   2 Awoke twice due to rhinosinusitis symptoms

   3 Awoke 3 times due to rhinosinusitis symptoms

   4 Was not able to sleep at all due to my rhinosinusitis symptoms

2. **How would you rate your ability to smell?**

   0 Not able to smell anything

   1 Can smell only strong odors

   2 Can smell some, but not all, odors

   3 Have no problem smelling

3. **How many puffs of rescue (albuterol/salbutamol) inhaler did you use last night? [For patients with comorbid asthma only]**

   [Patient will type in the number of puffs, patients that do not have comorbid asthma (i.e. were not ≥12% reversible at screening or in the year prior) will be instructed to enter 0]

PM QUESTIONS:

1. **Describe your rhinosinusitis symptoms today.**

   0 No noticeable rhinosinusitis symptoms

   1 Mild rhinosinusitis symptoms, barely noticeable

   2 Rhinosinusitis symptoms with exercise/exertion

   3 Rhinosinusitis symptoms with mild exertion

4 Almost constant difficulty due to my rhinosinusitis symptoms

2. Were your daily activities affected by your rhinosinusitis symptoms today?

0 No effect of rhinosinusitis symptoms on my daily activities

1 Activity was normal and only mildly affected by my rhinosinusitis symptoms

2 Activity was normal but moderately affected by my rhinosinusitis symptoms

3 Rhinosinusitis symptoms limited my activity to a significant degree

4 Rhinosinusitis symptoms severely restricted my daily activities

3. How would you rate your anterior rhinorrhea (the discharge draining from your nose, "runny nose") in the past 24 hours?

0 No noticeable discharge from my nose

1 Minor discharge from my nose, did not require tissues

2 Some discharge from my nose, required a few tissues

3 Significant discharge from my nose

4 Near constant discharge from my nose

4. How would you rate your posterior rhinorrhea (postnasal phlegm dripping into your throat) in the past 24 hours?

0 No noticeable postnasal drip

1 Some minor postnasal drip

2 Moderate postnasal drip

3 Significant postnasal drip

4 Near constant postnasal drip

5. Did you take your daily nasal steroid (mometasone) today? Yes/No

6. How many puffs of rescue inhaler did you use today? [For patients with comorbid asthma only]

[Patient will type in the number of puffs, patients that do not have comorbid asthma will be instructed to enter 0]

7.8.4 Daily Nasal Peak Inspiratory Flow (at Home)

All patients will be asked to perform nasal peak inspiratory flow (NPIF) testing at home BID and to record the results using the patient diary dispensed at Visit 1.

7.8.5 Computed Tomography (CT) Scan

Sinus CT scanning is used to assess fluid-filled or thick-membraned sinuses, to assess the extent of inflammation, to assess polyps and other growths in the airway, and to create a "map" of the patient's sinus cavities. An Imaging Manual will be provided separately to Study Sites that are approved and qualified to perform CT Scans. The Imaging manual will detail the equipment settings and requirements for scanning. The Imaging Manual will also detail the radiologic scoring of CT scans. All scans will be reviewed by blinded central over-read. Lund-Mackay Computed Tomography qualitative scores and quantitative analysis will be performed from patients enrolled at Study Sites that are approved and qualified to perform CT scans.

7.8.6 In-Clinic Pulmonary Function Tests (PFT)

Spirometry is required for only patients with comorbid asthma (i.e. demonstrating ≥12% reversibility at screening or in the 12 months prior). Spirometry (peak expiratory flow, forced vital capacity, and FEV_1) will be performed according to American Thoracic Society and the European Respiratory Society (ATS/ERS) Standardization of Spirometry (2019), with equipment operated by trained clinical staff.

Pulmonary function will be assessed in clinic or by home healthcare at the timepoints indicated in the Schedule of Assessment (Table 1).

7.8.7 Smell Test (UPSIT)

The UPSIT is a commercially available, validated smell test that has 40 items, where each item has 1 correct answer and 3 incorrect answers or "distractors". The test is a forced choice paradigm, that is, if an individual is unsure of an answer, they are forced to guess a response hence a score of 25% on average would reflect random guessing. An UPSIT result is scored out of 40 where a higher score indicates better olfaction. The test consists of 4 different 10-page booklets, with a total of 40 questions. On each page, there is a different "scratch and sniff" strip which is embedded with a microencapsulated odorant. There is also a 4-choice multiple choice question on each page. The scents are released using a pencil. After each scent is released, the patient smells the level and detects the odor from the 4 choices. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. The score is compared with scores in a normative database from 4000 normal individuals, this tells the level of absolute smell function. The score also indicates how the patient does in accordance to their age group and sex.

The test is occasionally judged to have an American cultural bias. There have been British, Chinese, French, German, Italian, Korean and Spanish UPSIT versions made which may be used depending on the countries in which the study is performed.

For the timepoints on which the UPSIT is administered, refer to the Schedule of Assessments (Table 1).

7.8.8 Visual Analog Scale for Rhinosinusitis (VAS-RS)

The Visual Analogue Scale for rhinosinusitis (VAS-RS) is a 10 cm scale that ranges from "no symptoms" to "worst symptoms ever" for each of the nasal symptoms (**Appendix A**). The VAS will direct the patient to mark a vertical line at the point that best corresponds to how bothersome their symptoms have been between visits the VAS-RS is collected.

For the timepoints on which the VAS-RS is assessed, refer to the Schedule of Assessments (Table 1).

7.8.9 Total Nasal Symptom Score (TNSS)

The Total Nasal Symptom Score (TNSS) is the sum of scores for each of nasal obstruction, nasal itching/sneezing, and Secretion/Runny nose (rhinorrhea), using a 4-point scale (0, 1, 2, 3), where 0 indicates no symptoms, a score of 1 for mild symptoms that are easily tolerated, 2 for awareness of symptoms which are bothersome but tolerable and 3 is reserved for severe symptoms that are hard to tolerate and interfere with daily activity (**Appendix B**). TNSS is calculated by adding the score for each of the symptoms to a total score out of 9.

For the timepoints on which the TNSS is assessed, refer to the Schedule of Assessments (Table 1).

7.8.10 Sino-Nasal Outcome Test (SNOT-22)

The Sino-Nasal Outcome Test (SNOT-22) is a 22-item list of symptoms and social/emotional consequences related to the patient's rhinosinusitis, using a 5-point scale (0,1,2,3,4,5), where score of 0 indicates No Problem, 2 for Very Mild Problem, 3 for Mild or Slight Problem, 4 for Moderate Problem, and 5 for Problem as bad as it can be. Patients will also be asked to mark the most important items that affect their health for a maximum of 5 out of the 22 items listed during the reporting period (**Appendix C**). A Minimal Clinically Important Difference (MCID) value for SNOT-22 total scores is defined as improvement of at least 8.9 points in patients with chronic rhinosinusitis (Hopkins C 2009).For the timepoints on which the SNOT-22 is assessed, refer to the Schedule of Assessments (Table 1).

7.8.11 EuroQoL Health Status Questionnaire (EQ-5D-5L)

The EuroQoL Health Status Measure, 5 Dimensions/5 Levels (EQ-5D-5L) is a well-validated, general health-related quality of life assessment tool published by the EuroQol Group. The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems,

severe problems and extreme problems. The patient is asked to indicate their health state by choosing the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ-VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. For the timepoints on which this questionnaire is administered, refer to the Schedule of Assessments (Table 1).

7.8.12 Healthcare Resource Utilization Questionnaire

The Healthcare Resource Utilization Questionnaire will be used to evaluate the patients' need for medical services related to symptoms of their chronic rhinosinusitis with nasal polyposis. This questionnaire will be completed by patients. For the timepoints on which this questionnaire is administered, refer to the Schedule of Assessments (Table 1).

7.8.13 Pharmacodynamic Endpoints

Blood will be collected from patients throughout the study as indicated in the Schedule of Assessments (Table 1), for measurement of biomarkers of inflammation associated with chronic rhinosinusitis with nasal polyposis.

7.8.14 Pharmacokinetic Assessments

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

7.8.15 Blood Volumes

The approximate blood volumes to be collected for safety laboratory tests, pregnancy test, PK, and PD are given in Table 3. These volumes may vary slightly based on regional differences in standard tube sizes. The total sample volumes over the course of the 32-week study will not exceed a safe and medically advisable amount in any given collection event.

Table 3 Blood Volumes

Assessment		Sample Volume (mL)	No. of Samples	Total Volume (mL)
Safety	Hematology	3	11	33
	Biochemistry	7.5	11	82.5
Human immunodeficiency virus/ hepatitis B surface antigen test		4	1	4
Pregnancy		5-7	1	5-7

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Pharmacokinetics	5-7	7	35-49
Pharmacodynamics	5-7	6	30-42
Antidrug antibody/ neutralizing antibody	3-5	5	15-25

8 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 IP, at any time after the patient signs the ICF until Visit 17 (End of Study) or an Early Termination Visit, whichever occurs first.

8.1.2 Serious Adverse Event

An AE 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 pre-existing 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 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.

If a diagnosis could be established, record the diagnosis as AE; If impossible to establish a diagnosis, record Signs and symptoms as AEs until a diagnosis could finally be determined, information including signs and symptoms of each AE should be described in detail, including

- Onset time and date
- Offset time and date
- Severity (mild, moderate, severe, life-threatening, death)
- Relationship to study drug (related, not related),
- Action taken with study drug (dose not changed, study drug interrupted, study drug withdrawn, not applicable, unknown)
- 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 whether or not 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. Medical Dictionary for Regulatory Activities (MedDRA) 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 Adverse Event Causality

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the eCRF, 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 IP 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 categories in Table 4.

Table 4. Adverse Event Causality

Causality Category	Description
Related	An adverse event 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 adverse event that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor. If the investigator cannot determine the etiology of the event but determines that IP did not cause the event, this should be clearly documented on the eCRF and SAE Report Form if applicable.

8.5 Assessment of Adverse Event 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 non-invasive intervention indicated or limiting age-appropriate instrumental activities of daily living (ADLs). Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc

- **Grade 3 / Severe or Medically Significant But Not Immediately Life-threatening**: hospitalization or prolongation of hospitalization indicated or disabling or limiting self-care ADLs. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden
- **Grade 4 / Life Threatening Consequences**: urgent intervention indicated.
- **Grade 5 / Death Related to AE**

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

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

8.6 Adverse Event of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. 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.

AESIs for this study:

- Conjunctivitis
- Keratitis
- Anaphylaxis (definition below)
- AE of injection site reaction lasting >24 hours (guidance below)
- AST/ALT elevated >5X ULN
- Parasitic and opportunistic infections
- Pregnancy
- Symptomatic overdose (i.e. overdose of study drug resulting in an adverse event)

Conjunctivitis and keratitis have been subjects of interest in the dupilumab experience. (Akinlade 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 1 AE of "conjunctivitis" while those patients in the placebo group (n = 517) reported 11 (2.1%) such events. Conjunctivitis AEs were mostly mild to moderate in severity with severe events reported in ≤ 0.5% of the dupilumab combined group vs. ≤ 0.3% of the placebo group. Two patients in the dupilumab group permanently discontinued study drug treatment due to a conjunctivitis event. Onset typically occurred during Weeks 4 to 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 CRSwNP.

Due to the dupilumab experience in atopic dermatitis, ophthalmic adverse events of "conjunctivitis" and "keratitis" will be considered AEs of Special Interest (AESI) 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 site 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 Appendix D as an aid in the assessment of common symptoms of injection site reactions. 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 Termination

Using CTCAE Version 5.0, patients 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 drug treatment 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 Parexel with copy to the Sponsor:

SAE Reporting email: NorthAmerica_Medical@Parexel.com

Copy to Sponsor: 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 AE 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:

- Patient ID number
- Country where event occurred
- Event Information
- List of relevant test results and laboratory data
- Any other relevant history
- Whether the study drug 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 case report form. The same nomenclature should be used on both the SAE report form and the AE case report form. 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 patient 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 patients with rhinosinusitis with nasal polyps and asthma. Because dupilumab is a marketed product in the same class that binds to the same target (IL4Ralpha), SAEs not currently reflective of safety presented in 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, FDA, and/or other competent 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 in the local legislation. Reporting will be to the European Medicines Agency and EU member states via Eudravigilance.

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). Spontaneous miscarriage and congenital abnormalities will be reported as an SAE and an SAE form should be submitted. Pregnancy itself is not an SAE. Female patients becoming pregnant during the study and after randomization must be immediately withdrawn from study drug 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 STATISTICAL METHODS

Complete details of the statistical analyses and methods, including data conventions, and any subgroup comparisons will be contained in a separate Statistical Analysis Plan.

9.1 Sample Size

The sample size estimation is based on the comparison between CBP-201 300 mg every 2 weeks vs. placebo with regard to the co-primary endpoint change from baseline in NPS at Week 24 (LIBERTY SINUS studies, Bachert et al 2019).

Assuming a common standard deviation in the NPS of 2.1, and based on the use of a two-sided test at the alpha=0.05 level of significance 41 patients per group will provide 80% power to detect a difference of

1.3 between the CBP-201 group and the placebo group in the change of NPS from baseline to Week 24. To allow for a 15% dropout rate, the planned samples size is 49 subjects per group (147 total).

- Roughly, to ensure at least 74 patients have co-morbid asthma: Recruitment of NP patient without co-morbid asthma will stop when approximately 70 patients without asthma are randomized, and
- Patients with co-morbid asthma will continue to be randomized to complete a total number of 147 randomized NP patients.

If greater than 15% of the treated patients do not complete the study, the sample size may be adjusted to ensure adequate power.

9.2 Analysis Populations

Five populations will be defined: Randomised Set (RS), Full Analysis Set (FAS), Per Protocol Set (PPS), Safety Set (SS), and PK Set (PKS). The efficacy analyses will be conducted according to the treatment to which the patients are randomized.

Randomised Set

The Randomised population consists of all patients who are randomized in the study to treatment.

Full Analysis Set

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 of study treatment and at least one primary endpoint datum collected during the treatment period.

Per Protocol Set

The Per Protocol Set, a subgroup of the FAS, includes patients without major protocol deviations. Supportive efficacy analyses will be conducted in the PPS population.

Safety Set

The analysis population for the safety endpoints will be the Safety Set. The Safety Set consists of all randomly assigned patients who received at least 1 dose of study treatment. These patients will be categorized according to the treatment they actually received.

Pharmacokinetic Set

The PK Set consists of all randomly assigned patients from whom at least 1 post-dose PK blood sample was collected. PD/PK relationships will be explored in a separate analysis plan and report.

9.3 Interim Analysis

There is no interim analysis planned for this study. The primary analysis is planned when the last patient completes Week 32 visit.

9.4 Statistical Methodology

All statistical tests will be 2-sided with a significance level of $\alpha = 0.05$, unless otherwise stated. Continuous variables will be summarized by descriptive statistics, including the number of patients, mean, standard deviation (SD), median, minimum, maximum, and the geometric mean, where appropriate. Categorical variables will be presented with the frequency and percentage in each category by treatment group. Specific statistical methodology will be provided in the Statistical Analysis Plan to be completed before the unblinding of the study data.

9.5 Efficacy Analysis

9.5.1 Co-Primary Endpoints and Efficacy Analysis

Endoscopic NPS

A linear mixed model will be applied to change from baseline to each timepoint through Week 24 in endoscopic NPS. The fixed effects will include treatment group, endoscopic NPS at baseline, visit, interaction between treatment group and visit, and the presence of comorbid asthma in the model. Patient will be included as random effect. The covariance matrix applied to the within-subject error will be estimated by Restricted maximum likelihood (REML). The Kenward-Roger approximation will be used to estimate the degree of freedom. Details of assumption on variance structure will be described in the SAP.

Average Daily NCS

A similar linear model will be used to analyze average daily nasal congestion score (NCS).

Using these two models, the primary analysis for each primary endpoint will compare the CBP-201 Q2W 300 mg group to the placebo group using a two-sided test at the alpha=0.05 level of significance. "Study success" is defined as a statistically significant result for both of the co-primary endpoints.

9.5.2 Secondary Analyses

Using the same models described in Section 10.3.1, the comparisons between the CBP-201 Q4W 300 mg group to the placebo group using a two-sided test at the alpha=0.05 level of significance. "Study success" for the Q4W group is defined as a statistically significant result for both of the co-primary endpoints.

However, if the primary analysis is not statistically significant for one or both of the two co-primary endpoints, the results from the secondary analysis will be exploratory rather than confirmatory.

The similar analyses to endoscopic NPS will be performed for each secondary continuous variable:

- Percentage of maxillary sinus volume occupied by disease on CT and Lund-Mackay Computed Tomography scores from patients enrolled at Study Sites that are approved and qualified to perform CT scans
- University of Pennsylvania Smell Identification Test (UPSIT)
- Visual analogue scale for rhinosinusitis (VAS-RS)
- Total nasal symptom score (TNSS)
- 22-item Sinonasal Outcome Test (SNOT-22)
- Average daily anterior rhinorrhea score
- Average daily posterior rhinorrhea score
- Average daily loss of smell score
- Daily subject-assessed nasal peak inspiratory flow (NPIF)

Proportion of patients requiring rescue treatment (systemic CS for > 5 consecutive days) or having had surgery for nasal polyps through Week 24 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. The Cochran-Mantel-Haenszel (CMH) test adjusted by comorbid asthma will be performed to compare the proportion between each CBP-201 group and placebo group.

The Kaplan-Meier plot will be presented for the time to rescue treatment (systemic CS for >5 consecutive days) or surgery for nasal polyps through Week 24. Median of the time and the corresponding 95% CI will be calculated for each treatment group. The event-free rate at Week 24 week will be presented with 95% CI. Log-rank test will be performed to compare the event free distribution 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.

9.5.3 Exploratory Analyses

Exploratory analyses will be done using a similar model to the primary endoscopic NPS endpoint analysis. Endpoints will include:

- Change from baseline at Week 24 in FEV1 for subjects with asthma
- Proportion of patients with minimal clinically important difference $\geq$ 8.9 in SNOT-22 at Week 24
- Change from baseline at Week 16 in endoscopic NPS
- Change from baseline at Week 16 in Average daily NCS
- Change from baseline at Week 24 in European quality of life scale (EQ 5D-5L)
- Healthcare resource utilization through Week 24

9.6 Safety Data Analysis

Adverse events will be coded using the MedDRA. Treatment-emergent adverse events (TEAEs) are defined as any AEs occurred or worsen during the treatment period from first administration of study treatment to end of the follow-up period, whether or not 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, AESIs and adverse events resulting in discontinuation from the study will be summarized by treatment group.

Safety laboratory parameters, ADA and NAb, vital signs, ECG parameters will be summarized by treatment group and by scheduled visit. Change from Baseline in these continuous parameters will also be summarized by treatment group and by scheduled visit.

For AESI, the percentage of subjects 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 subjects 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.

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, in order 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.

9.7 Missing Data

Handling of missing data will be detailed in the SAP.

For the primary analyses, missing values at week 24 will be imputed using methods detailed in the SAP. In brief, the primary analysis would be MMRM (mixed model repeated measures) which will be performed to mitigate the impact of missing data. This approach assumes that missing observations are missing-at-random (missingness is related to observed data) during the study and borrows information from patients in the same treatment arm taking into account both the missingness of data and the correlation of the repeated measurements. All secondary and exploratory efficacy analyses may be conducted using similar imputation for missing values as detailed in the SAP.

Safety analyses, will be conducted using available data with no imputation for missing values.

9.8 Sensitivity Analysis

Sensitivity analyses will be conducted to confirm the robustness of the results for the primary analyses. These may include pattern mixture model-multiple imputation (PMM-MI), control-based PMM-MI with analysis of covariance (ANCOVA) model and/or tipping point analyses, as appropriate. The details will be outlined in the SAP.

9.9 Multiplicity Considerations

The use of a fixed sequence testing procedure for the primary analyses controls the overall level of significance for these confirmatory analyses. All other analyses will be conducted using two-sided tests at the alpha=0.05 level of significance, with no control for multiplicity.

9.10 Pharmacokinetic Analysis

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.

Additional sampling will be obtained after the last treatment dose, as noted in the schedule of assessments (Table 1), to characterize the return to Baseline.

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

9.11 Pharmacodynamic Analysis

Pharmacodynamic endpoint analyses will be considered exploratory. PD endpoints including IgE, ECP, TARC, eosinophil count, Eotaxin-3, and periostin in the blood will be summarized by treatment group. Exploratory PK/PD analyses will be detailed in a separate analysis plan and report.

9.12 Demographic and Medical History

Demographic characteristics (eg, sex, age, weight, height, ethnicity) and medical history with disease-relevant baseline characteristics (eg, LMK CT score, NPS, NCS, NPIF, pulmonary function, baseline symptom scores) will be summarized by treatment group. All other baseline characteristics will be summarized by treatment group.

9.13 Analysis of Concomitant Medication Use

Concomitant medications will be coded according to the WHODrug. Concomitant medications will be summarized overall and by drug classification by treatment group.

9.14 Analysis of Exposure to Study Drug

The duration of exposure will be calculated using the first and last day of study drug dosing. A summary of the duration will be presented by treatment group.

9.15 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.

10 DATA HANDLING AND QUALITY ASSURANCE

10.1 Case Report Forms

Study data is recorded using an eCRF via the Medidata RAVE system provided by the contracted CRO. The overall procedures for quality assurance of clinical study data including data collection and management, are described in the Data Management Plan (DMP).

Study data will be entered in the eCRF via Electronic Data Capture (EDC) by clinical research staff at each clinical site from the source documents.

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 or if a pandemic-related quarantine prevents in-person access) at the request of the Sponsor or its designee and only if there is an appropriate SOP is in place to ensure data integrity and patient privacy in the case of such a transfer.

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 CRO's 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 the CRO and the Sponsor, for compliance with applicable government regulation with respect to current 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, the CRO, the FDA, or other regulatory agencies 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 IP. 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 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, the FDA, 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 any 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. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICFs 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 their 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 nonadherence to FDA 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 their 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 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
- Reading and understanding the CBP-201 Investigator's Brochure version 5
- 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 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, fully executed, and all updates on a newly executed Form FDA 1572
- Curriculum vitae (CV) for the Principal Investigator and each Sub-Investigator will be listed on Form FDA 1572 (US) or ICH E6.4. 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
- Providing laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493

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 CONNECT, 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 electronic data capture 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 INVESTIGATOR'S STATEMENT

I agree to conduct the study as outlined in the protocol entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate CBP-201 in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps" in accordance with the guidelines and all applicable government regulations including US Part 54 of Title 21 of the CFR. I have read and understand all sections of the Protocol, including Section 11 ADMINISTRATIVE CONSIDERATIONS.

Protocol Version 3.0

Date: 21 December 2021

Principal Investigator's Signature	Date
Principal Investigator's Name	Site ID

13 REFERENCES

Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, Prens E, Asbell P, Akpek E, Corren J, Bachert C, Hirano I, Weyne J, Korotzer A, Chen Z, Hultsch T, Zhu X, Davis JD, Mannent L, Hamilton JD, Teper A, Staudinger H, Rizova E, Pirozzi G, Graham NMH, Shumel B, Ardeleanu M, Wollenberg A. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019 Sep;181(3):459-473.

Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MS, Thompson BR; on behalf of the American Thoracic Society and the European Respiratory Society. Standardization of Spirometry 2019 Update An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med Vol 200, Iss 8, pp e70–e88, Oct 15, 2019

Avdeeva K, Fokkens W. Precision medicine in chronic rhinosinusitis with nasal polyps. Curr Allergy Asthma Rep. 2018;18(4):25. doi:10.1007/s11882-018-0776-8.

Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA. 2016;315:469-479.

Bachert C, Han JK, Desrosiers M, Hellings P, Amin N, Lee SE, Mullol J, Greos L, Bosso J, Laidlaw TM, Cervin A, Maspero JF, Hopkins C, Olze H, Canonica GW, Paggiaro P, Cho SH, Fokkens WJ, Fujieda S, Zhang M, Lu X, Fan C, Draikiwicz S, Kamat SA, Khan A, Pirozzi G, Patel N, Graham NMH, Ruddy M, Staudinger H, Weinreich D, Stahl N, Yancopoulos GD, Mannent LP. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394: 1638–50.

Cardell L-O, Stjärne Pär, Jonstam K, Bachert C. Endotypes of chronic rhinosinusitis: Impact on management. J Allergy Clin Immunol. 2020;145:752-756.

Dupixent (dupilumab) injection, for subcutaneous use; Reference ID 4454337; June 2019; available at: https://www.accessdata.fda.gov/scripts/cder/daf/.

Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gabory L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kalogjera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Meco C, Matricardi PM, O'Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia P, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdinic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kawauchi H, Kjeldsen A, Klimek L, Krzeski A, Kopacheva Barsova G, Kim SW, Lal D, Letort JJ, Lopatin A, Mahdjoubi A, Mesbahi A, Netkovski J,

Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Otori N, Ouennoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepageran N, Psaltis A, Pugin B, Raftopulos M, Rombaux P, Riechelmann H, Sahtout S, Sarafoleanu CC, Searyoh K, Rhee CS, Shi J, Shkoukani M, Shukuryan AK, Sicak M, Smyth D, Snidvongs K, Soklic Kosak T, Stjarne P, Sutikno B, Steinsvag S, Tantilipikorn P, Thanaviratananich S, Tran T, Urbancic J, Valiulius A, Vasquez de Aparicio C, Vicheva D, Virkkula PM, Vicente G, Voegels R, Wagenmann MM, Wardani RS, Welge-Lussen A, Witterick I, Wright E, Zabolotniy D, Zsolt B, Zwetsloot CP. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600. PMID: 32077450.

Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in South Korea according to diagnostic criteria. Rhinology. 2011;66:1216-1223.

Hirsch AG, Stewart WF, Sundaresan AS, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy. 2017;72:274-281.

Kim JH, Cho C, Lee EJ, et al. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. Rhinology. 2016;54:329-335.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97).

Scadding GK, Durham SR, Mirakian R, Jones NS, Drake-Lee AB, Ryan D, Dixon TA, Huber PAJ, and Nasser SM. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. Clin Exp Allergy 38:260-275.

Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, Bartalesi F, Lipman M, Mariette X, Lortholary O, Weinblatt ME, Saag M, and Smolen J. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015 74:2107-2116.

Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447–454.

14 APPENDICES

APPENDIX A – VISUAL ANALOG SCALE – RHINOSINUSITIS (VAS-RS)

*DO NOT make photocopies of this document. Only use printed copies provided by Parexel.

INSTRUCTIONS TO SITE PERSONNEL: 1) Complete the date and time. 2) Verbally ask the subject to place a vertical mark at a place on the 10 cm line that represents the severity of each symptom over the past month. 3) Using the provided ruler, measure in centimeters from None to where the subject draws a line and enter that value in the right-most column		**SITE PERSONNEL ENTER RESPONSES IN THIS COLUMN** DATE: _____ MMM/DD/YYYY TIME: _____ hh:mm (24 hour time format)
INSTRUCTIONS TO PATIENT: Please draw **one vertical line** at the point that best corresponds to how bothersome the following symptoms were within the last month. Example:	None — More than I can imagine	
Total sinus symptoms	None — More than I can imagine	_____ Centimeters
Nasal blockage	None — More than I can imagine	_____ Centimeters
Headache /pressure on the face	None — More than I can imagine	_____ Centimeters
Loss of smell	None — More than I can imagine	_____ Centimeters
Post-nasal drip (secretions from the nose down to the throat)	None — More than I can imagine	_____ Centimeters
Runny nose	None — More than I can imagine	_____ Centimeters
Itchy eyes	None — More than I can imagine	_____ Centimeters
Itchy nose	None — More than I can imagine	_____ Centimeters
Sneezing	None — More than I can imagine	_____ Centimeters
Tearing	None — More than I can imagine	_____ Centimeters
Cough	None — More than I can imagine	_____ Centimeters
Tightness/pressing sensation on the chest	None — More than I can imagine	_____ Centimeters
Shortness of breath/difficulty with breathing	None — More than I can imagine	_____ Centimeters
Wheezing	None — More than I can imagine	_____ Centimeters

APPENDIX B – TOTAL NASAL SYMPTOM SCORE (TNSS)

Please answer all questions to the best of your ability. This information will help us understand and treat symptoms.

Please rate the following rhinitis symptoms during the past week:

1. Nasal obstruction

No symptoms	0
Mild – Awareness of the symptom but not troublesome	1
Moderate – Troublesome but does not interfere with usual daily activities or sleep	2
Severe – Interferes with usual daily activities or sleep	3

2. Itching/Sneezing

No symptoms	0
Mild – Awareness of the symptom but not troublesome	1
Moderate – Troublesome but does not interfere with usual daily activities or sleep	2
Severe – Interferes with usual daily activities or sleep	3

3. Secretion/Runny nose

No symptoms	0
Mild – Awareness of the symptom but not troublesome	1
Moderate – Troublesome but does not interfere with usual daily activities or sleep	2
Severe – Interferes with usual daily activities or sleep	3

Total score: _____
9

APPENDIX C – Sino-Nasal Outcome Test-22 QUESTIONNAIRE (SNOT-22)

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	**0**	**1**	**2**	**3**	**4**	**5**		○
2. Nasal Blockage	**0**	**1**	**2**	**3**	**4**	**5**		○
3. Sneezing	**0**	**1**	**2**	**3**	**4**	**5**		○
4. Runny nose	**0**	**1**	**2**	**3**	**4**	**5**		○
5. Cough	**0**	**1**	**2**	**3**	**4**	**5**		○
6. Post-nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
7. Thick nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
8. Ear fullness	**0**	**1**	**2**	**3**	**4**	**5**		○
9. Dizziness	**0**	**1**	**2**	**3**	**4**	**5**		○
10. Ear pain	**0**	**1**	**2**	**3**	**4**	**5**		○
11. Facial pain/pressure	**0**	**1**	**2**	**3**	**4**	**5**		○
12. Decreased Sense of Smell/Taste	**0**	**1**	**2**	**3**	**4**	**5**		○
13. Difficulty falling asleep	**0**	**1**	**2**	**3**	**4**	**5**		○
14. Wake up at night	**0**	**1**	**2**	**3**	**4**	**5**		○
15. Lack of a good night's sleep	**0**	**1**	**2**	**3**	**4**	**5**		○
16. Wake up tired	**0**	**1**	**2**	**3**	**4**	**5**		○
17. Fatigue	**0**	**1**	**2**	**3**	**4**	**5**		○
18. Reduced productivity	**0**	**1**	**2**	**3**	**4**	**5**		○
19. Reduced concentration	**0**	**1**	**2**	**3**	**4**	**5**		○
20. Frustrated/restless/irritable	**0**	**1**	**2**	**3**	**4**	**5**		○
21. Sad	**0**	**1**	**2**	**3**	**4**	**5**		○
22. Embarrassed	**0**	**1**	**2**	**3**	**4**	**5**		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

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