Parexel International

Suzhou Connect Biopharmaceuticals Ltd.

CBP-201-WW003

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

Statistical Analysis Plan

Version: 2.0

Parexel Project Number: 257643

Note that the date below is effective date of the CRO SAP TEMPLATE document

SAP Signatures applied to last page in Veeva Vault document management

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

Daniel Miconi Date

Senior Manager, Clinical Operations

Suzhou Connect Biopharmaceuticals Ltd.

_____ _____

Jang Yun, PhD Date

Senior Director of Biostatistics, Clinical Operations

Suzhou Connect Biopharmaceuticals Ltd.

Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	Amy Kim Project Role: Lead Biostatistician
Reviewer	Bazou Kone Project Role: Biostatistician

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
0.1	15-Jun-2021	New document
0.2	14-Jul-2021	Updated per Connect team review
1.0	30-Jul-2021	Updated per CRM especially adding sensitivity analysis for use of rescue medication and statistical analysis for proportion of patients with minimal clinically important difference ⩾ 8.9 in SNOT-22 at Week 24. Also subgroup analyses were added and minor language was updated in rescue medication per client request
1.1	18-Jan-2022	Updated per protocol amendment v3.0 and internal/Connect team review
1.2	25-Jan-2022	Updated per Connect team review
1.3	19-May-22	Updated to include change due early termination of the study.
1.4	15-Jun-22	Updated section 4.3.1 and section 4.15

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR(1)	First-order Autoregressive
AST	Aspartate Aminotransferase
BID	twice daily
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CS	Compound Symmetry
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECP	Eosinophil Cationic Protein
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol Health Status Measure, 5 Dimensions/5 Levels
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in the first second of expiration
GGT	Gamma-Glutamyltransferase
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface antibody

Abbreviation / Acronym	Definition / Expansion
HBsAg	Hepatitis B surface Antigen
HCVAb	Hepatitis C virus antibody
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid(s)
IgE	Immunoglobulin E
IL	Interleukin (IL-4, IL-13, etc)
INCS	Intranasal Corticosteroid
LABA	Long-Acting ß-Agonist
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered Dose Inhaler
MFNS	Mometasone Furoate Nasal Spray
MMRM	Mixed-effect Model for Repeated Measures
MNAR	Missing Not at Random
NAb	Neutralizing Antibody
NCS	Nasal Congestion Score
NPIF	Nasal Peak Inspiratory Flow
NPS	Nasal Polyp Score
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Set
PD	Pharmacodynamic(s)
PMM-MI	Pattern Mixture Model Multiple Imputation
PPS	Per Protocol Set
PROs	Patient-Reported Outcomes
PT	Preferred Term
SABA	Short-Acting ß-agonist

Abbreviation / Acronym	Definition / Expansion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
SS	Safety Set
TARC	Thymus and Activation-Regulated Chemokine
TEAE	Treatment-Emergent Adverse Event
TNSS	Total Nasal Symptom Score
TOEP	Toeplitz
ULN	Upper Limit of Normal
UN	Unstructured
UPSIT	University of Pennsylvania Smell Identification Test
VAS-RS	Visual Analogue Scale for Rhinosinusitis
VS	Vital Signs
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

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 Chronic rhinosinusitis with nasal polyps (CRSwNP) to assess both efficacy and safety of CBP-201.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the tables, listings, and figures. It describes the variables, analysis populations, anticipated data manipulations and other details of the analyses not provided in the protocol.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (December 21, 2021)
- electronic Case Report Form (eCRF), Version 6.0 (September 03, 2021)

The structure and content of the SAP are based upon the International Conference on Harmonisation (ICH) E3 – Guideline for Industry Structure and Content of Clinical Study Reports.

Pharmacokinetic analyses will be described in a separate document.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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 Objective(s)

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 Objective(s)

To evaluate:

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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 three periods:

- Screening/Run-In Period: 4 weeks
- Treatment Period: CBP-201/Placebo for 24 weeks
- Post-Treatment Follow-Up Period: 8 weeks

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 randomized patients will be targeted to have comorbid asthma, defined as ≥12% reversibility (improvement in FEV_1) and use of ICS < 1000 µg/day, and treatment will be stratified on a presence of comorbid asthma.

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

After screening/run-in has been complete, eligible patients will be stratified by presence of comorbid asthma and 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.

A detailed schedule of assessments for the study is provided in 3.2.

3.2 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 2-hour 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, then 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 retrained, if necessary, on the use of the patient diary device and NPIF meter.
k. A questionnaire of Health Care Resource Utilization. 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.

3.3 Endpoints

3.3.1 Efficacy Endpoints

3.3.1.1 Co-primary Efficacy Endpoints

There will be two co-primary endpoints:

- Change from baseline at Week 24 in endoscopic NPS
    - Endoscopic NPS score 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)

3.3.1.2 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 Centers 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 (from diary)
    - Average daily posterior rhinorrhea score (from diary)
    - Average daily loss of smell score (from diary)
    - Daily subject-assessed Nasal Peak Inspiratory Flow (NPIF)
- Requirement of rescue treatment (systemic corticosteroid for > 5 consecutive days) or having had surgery for nasal polyps through Week 24
- Time to rescue treatment (systemic corticosteroid for > 5 consecutive days) or surgery for nasal polyps through Week 24

3.3.1.3 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 ≥ 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

3.3.1.4 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.]

3.3.1.5 Pharmacokinetic Endpoints

Whole blood for plasma CBP-201 concentrations will be obtained and analyzed. 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.
The details of PK analysis will be reported in a separate PK analysis plan.

3.3.1.6 Safety Endpoints

- Adverse events (AEs) reported, including serious adverse events (SAEs) and adverse events of special interest (AESI)
- Vital signs (body temperature, respiratory rate, blood pressure, and heart rate)
- Physical examinations
    - Complete: 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
    - Brief: general appearance, eyes, lungs, lymph nodes
- 12-lead electrocardiogram (ECG) parameters
- Injection site evaluations
- Safety laboratory parameters (urinalysis, serum chemistry, and hematology)
- Antidrug antibodies (ADA) and neutralizing antibodies (NAb)

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, listings, and figures to be included in the report will be independently checked by biostatistician for consistency, integrity and in accordance with standard Parexel procedures.

4.2 Definitions

Age at Baseline
Age will be calculated using the date of birth and date of the baseline visit as below:

Integer part of [(Date of Baseline Visit – Date of Birth) / 365.25]

Baseline
Unless otherwise specified, baseline is defined as the last non-missing value prior to the first dose of study drug. If time is not collected but the assessment is performed on the same day as the first dose of study drug, it would be considered as baseline.

Baseline Week
For weekly average analysis, baseline week is defined as 7 days prior to the baseline visit (Study day ranges from -7 to -1).

Change from Baseline
Change from baseline is defined as post-baseline value minus baseline value.

Study Day 1
Study day 1 is defined as the date of randomization for untreated randomized subjects or the date of first dose for treated subjects.

Study Day
Study Day will be calculated relative to the date of randomization for untreated randomized subjects and relative to the date of first dose for treated subjects.

If event is prior to the first dose, then study day is calculated as:

Date of Event – Date of First Dose

If event is after the first dose, then study day is calculated as:

Date of Event – Date of First Dose + 1

Duration of Treatment
Duration of Treatment (days) will be calculated as:

Last Date of Dose – First Date of Dose + 1

Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as any adverse events occurred or worsen during the treatment-period, whether considered related to the treatment.

Where the AE start date is missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

Prior and Concomitant Medication
Prior and concomitant medication is defined as any medications that started before the first dose of study drug and stops on or after the first dose of study drug.

Prior Medication
Prior medication is defined as any medications that started and stopped before the first dose of study drug.

Concomitant Medication

Concomitant medication is defined as any medications that started on or after the first dose of study drug.

Treatment Compliance
Treatment compliance (%) will be calculated as:

$$\frac{\text{Total Amount of Study Drug Administered (mL)}}{\text{Total Amount of Study Drug Planned (mL)}} \times 100\%$$

4.3 General Presentation Considerations

Continuous data that are assumed to be normally distributed will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place, and the SD (and the standard error [SE], if applicable) will be reported to two more decimal places, than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.
Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place except 100%. 100% will be presented as 100% instead of 100.0%. Percentages will not be presented for zero counts. Percentages will be calculated using the number of subjects (n) as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. A missing category shall be included only for categorical variables where no data is available. The missing category will be omitted if there were no missing values for that variable.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Laboratory values contain '≥ x' or 'x ≤' will be taken as the value of x in the analysis. If a laboratory value contains 'y <' then y minus 0.001 will be used for the analysis. If a laboratory value contains 'z >' then z plus 0.001 will be used for the analysis.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001". P-values greater than 0.999 will be presented as ">0.999".

Confidence intervals will be presented to one more decimal place than the raw data.

4.3.1 Analysis Window

For visits that occur on or after the first dose of study treatment, study day is defined as date of event – date of first dose of study treatment + 1. For visits that occur prior to the first dose of study treatment, study day is defined as date of event – date of first dose of study treatment. There is no study day 0 defined for this study.

Table 1. Analysis Window for Safety Parameters

Nominal Visit	Analysis Visit	Target Study Day	Minimum Study Day	Maximum Study Day
Visit 2	Baseline	1	-30	1
Visit 3	Week 1	8	2	11
Visit 4	Week 2	15	12	18
Visit 5	Week 4	29	26	32
Visit 6	Week 6	43	40	46
Visit 7	Week 8	57	54	60
Visit 8	Week 10	71	68	74
Visit 9	Week 12	85	82	88
Visit 10	Week 14	99	96	102
Visit 11	Week 16	113	110	116
Visit 12	Week 18	127	124	130
Visit 13	Week 20	141	138	144
Visit 14	Week 22	155	152	158
Visit 15	Week 24 (End of Treatment)	169	166	172
Visit 16	Week 28	197	192	202
Visit 17	Week 32 (End of Study)	225	220	230

Table 2. Analysis Window for CT Scan

Nominal Visit	Analysis Visit	Target Study Day	Minimum Study Day	Maximum Study Day
Visit 2	Baseline	1	-30	1
Visit 15	Week 24 (End of Treatment)	169	166	172

Table 3. Analysis Window for NPS, VAR-RS, SNOT-22, and TNSS

Nominal Visit	Analysis Visit	Minimum Study Day	Maximum Study Day
Visit 2	Baseline	-7	-1
Visit 3	Week 1	1	8
Visit 4	Week 2	9	15
Visit 5	Week 4	23	29
Visit 7	Week 8	51	57
Visit 9	Week 12	79	85
Visit 11	Week 16	107	113
Visit 13	Week 20	135	141

Visit 15	Week 24 (End of Treatment)	163	169
Visit 17	Week 32 (End of Study)	219	225

Table 4. Analysis Window for Efficacy Parameters – Weekly average

Nominal Visit	Analysis Visit	Minimum Study Day	Maximum Study Day
Visit 2	Baseline	-7	-1
Visit 3	Week 1	1	8
Visit 4	Week 2	9	15
Visit 5	Week 4	23	29
Visit 6	Week 6	37	43
Visit 7	Week 8	51	57
Visit 8	Week 10	65	71
Visit 9	Week 12	79	85
Visit 10	Week 14	93	99
Visit 11	Week 16	107	113
Visit 12	Week 18	121	127
Visit 13	Week 20	135	141
Visit 14	Week 22	149	155
Visit 15	Week 24 (End of Treatment)	163	169
Visit 16	Week 28	191	197
Visit 17	Week 32 (End of Study)	219	225

Table 5. Analysis Window for Other Efficacy Parameters

Nominal Visit	Analysis Visit	Minimum Study Day	Maximum Study Day
Visit 2	Baseline	-7	-1
Visit 3	Week 1	1	8
Visit 4	Week 2	9	15
Visit 5	Week 4	23	29
Visit 6	Week 6	37	43
Visit 7	Week 8	51	57
Visit 8	Week 10	65	71
Visit 9	Week 12	79	85
Visit 10	Week 14	93	99
Visit 11	Week 16	107	113
Visit 12	Week 18	121	127
Visit 13	Week 20	135	141
Visit 14	Week 22	149	155

Visit 15	Week 24 (End of Treatment)	163	169
Visit 16	Week 28	191	197
Visit 17	Week 32 (End of Study)	219	225

If more than one assessment is available within the same analysis visit, the assessment with closest study day to the target study day will be reported for the analysis window. If two observations exist with the same distance to the target study day, then the first observation will be used.

Unscheduled visit will not be used in the analysis if scheduled visit is available. Unscheduled visit will be used in the analysis only if scheduled visit is not available.

4.3.2 Handling of Incomplete Dates

Every effort will be undertaken to avoid any missing or incomplete data, and missing data will not be imputed unless specified. If variables are imputed, the analysis dataset will contain a new variable with imputed value and the original variable will contain the original missing value.

Inevitable partial dates will be imputed for start/end dates of AEs or concomitant medications.

Incomplete dates of medical history will not be imputed.

Partial AE Start Date

- If only day is missing, then it will be set to:
  - First day of the month that the AE occurred, if month/year of the AE start date is different than the month/year of the first dose date.
  - The day of first dose date, if month/year of the AE start date is the same as month/year of the first dose date and month/year of the AE end date is different.
  - The day of first dose date or day of AE end date, whichever is earliest, if the month/year of the AE start and month/year of the first dose date and month/year of the AE end date are the same.
- If only month is missing, then it will be set to the earliest of the following:
  - January, as long as this date is after the first dose date
  - Month of the first dose date, if this date is the same day and year that the AE occurred
- If the day and month are both missing, then it will be set to the earliest of the following:
  - January 1 of the year, as long as this date is after the first dose date
  - Month and day of the first dose date, if this date is the same year that the AE occurred
  - The AE end date
- If dates are completely missing, then no imputation will be made.

Partial AE End Date

- If only day is missing, then it will be set to the earliest of the last follow-up date, last day of the month, or the date of death.
- If only month is missing, then it will be set to the earliest of the last follow-up date, December, or the date of death.

- If year is missing or AE is ongoing, the end date will not be imputed.
- If dates are completely missing, then no imputation will be made.

If the imputed AE end date is before the corresponding AE start date, then the AE end date will be set to the AE start date.

The same rule above will be applied to the start and end dates of concomitant medications.

4.4 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.5 Study Subjects

4.5.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

Subject disposition will be summarized by treatment and overall for:

- Number of subjects screened
- Number of subjects with screen failure
- Number of subjects randomized
- Number and percentage of subjects received at least one dose of study drug
- Number and percentage of subjects discontinued from study drug and primary reason for premature discontinuation
- Number and percentage of subjects discontinued from study and primary reason for premature discontinuation

By-subject listings of disposition details will also be provided.

4.5.2 Protocol Deviations

Protocol deviations will be classified as “major” or “minor” on ongoing basis by the clinical study team and sponsor.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the subject’s right, safety, well-being, and/or the validity of the data for analysis. Minor protocol deviations include all deviations from the protocol excluding the major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

The number and percentage of subjects with a major protocol deviation on Full Analysis Set by treatment and overall will be summarized. By-subject listing of all protocol deviations will also be provided.

4.6 Analysis Populations

<u>Randomised Set</u>

The Randomised Set consists all subjects who are randomized to treatment.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of randomized subjects who received at least 1 dose of study treatment and at least one primary endpoint datum collected during the treatment period. These subjects are grouped based on the treatment group to which were randomized. If a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as randomized' i.e. by randomized treatment group. The efficacy summaries and analyses will be based on the Full Analysis Set (FAS), which is based upon the Intention-to-Treat principle.

Per Protocol Set (PPS)

The Per Protocol Set (PPS) is defined as a subgroup of patients in FAS without major protocol deviations. A sensitivity analysis will be performed on the Per Protocol Set to assess the robustness of the study conclusions to the choice of analysis set for the primary efficacy variable.

Safety Set (SS)

The Safety Set (SS) is defined as 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. If a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as treated' i.e. by allocated treatment group. The safety summaries and analyses will be based on the Safety Set.

Pharmacokinetic Set (PKS)

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

An analysis population classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by Suzhou Connect Biopharmaceutical Ltd.

The number and percentage of subjects in each analysis set by treatment group and overall will be summarized on Randomised Set. By-subject listing of analysis population assignment will also be provided.

4.7 Demographic and Other Baseline Characteristics

Age at baseline (years), gender, race, ethnicity, geographic region, height (cm) at Baseline, weight (kg) at Baseline, presence of comorbid asthma at Baseline, type 2 inflammation at Baseline marked by Baseline blood eosinophil count ≥ 300 cells/μL, endoscopic NPS at Baseline, average daily NCS at Baseline week, LMK CT score at Baseline, NPIF at Baseline, and FEV1 at Baseline for asthma patients will be summarized on Full Analysis Set by treatment and overall.

By-subject listing of demographic and other baseline characteristics will also be provided.

4.8 Medical History

Medical history at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and summarized on Safety Set by treatment and overall using system organ class and preferred term. By-subject listing of medical history will also be provided.

4.9 Prior and Concomitant Medication

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only as defined in 4.2. Medications starting after the completion/withdrawal date will not be classified or summarized.

Incomplete start and end date of the medications will be imputed as described in **Error! Reference source not found.**.

Concomitant medications and Prior and Concomitant medications will be coded using the World Health Organization Drug (WHODrug) Global March 2021 B3 and summarized on Safety Set by treatment and overall. Subjects with more than one medication in a given ATC level and preferred term will be counted only once.

By-subject listings of prior and concomitant medications will also be provided.

4.10 Treatment Compliance

Treatment compliance (%) is calculated as described in 4.2. A summary of the treatment compliance at each visit and overall treatment period will be provided on Safety Set by treatment and overall. By-subject listing of treatment compliance will also be provided.

4.11 Efficacy Evaluation

4.11.1 Statistical Analysis and Data Conventions

Unless otherwise specified, all statistical tests will be interpreted at a 2-sided significance level of 0.05 and all CIs at a 2-sided level of 95%. The overall type I error rate is 0.05 (two-sided) for the primary and secondary efficacy hypotheses.

4.11.1.1 Adjustments for Covariates

The primary and secondary efficacy analysis will be adjusted for the following baseline covariates:

1. Presence of comorbid asthma (stratification factor)
2. Endoscopic NPS at baseline (baseline measure of the primary efficacy variable)

For each covariate, a statistical test for the presence of a treatment-by-covariate interaction will be performed, by including the interaction term in the primary analysis model. If any of the treatment-by-covariate interactions are found to be statistically significant at the 5% level ($p<0.05$), subgroup analyses will be performed to further explore the nature of the interaction. In such cases, conclusions based on the primary analysis (no interaction) will be interpreted with caution.

4.11.1.2 Handling of Missing Efficacy Data

For primary analysis, MMRM 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 as well as safety analyses will be conducted without imputation of missing values.

To assess the robustness of the study conclusions to the choice of imputation method, the sensitivity analyses will be performed for the primary variable (see 4.11.3).

4.11.1.3 Multiple Comparisons/Multiplicity

The primary analysis 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. If both of the co-primary endpoints are statistically significant (p-value<0.05) then the same model as described 0 will be used for the key secondary analysis to compare the CBP-201 Q4W 300 mg group to placebo group using a two-sided test at the alpha=0.05 level of significance.

The definition of study success and use of a fixed sequence testing procedure for the primary analyses controls the overall level of significance. Hence there is no formal control for multiplicity planned.

4.11.1.4 Interim Analyses

No interim analyses are planned.

4.11.1.5 Examination of Subgroups

Baseline characteristics, all efficacy (including primary, secondary, and exploratory), safety, and PK/PD endpoints will be examined for the following subgroups:

- Ethnicity: Asian vs Non-Asian
- Country: Chinese vs Non-Chinese

Summaries of baseline characteristics, efficacy and safety endpoints by treatment group and subgroup will be produced. No sensitivity analysis will be performed within subgroup. No formal statistical analysis will be performed within subgroup.

Details of PK subgroup analysis will be provided by a separate PK analysis plan.

4.11.2 Co-primary Efficacy Analysis

The co-primary endpoints for the assessment of efficacy are the change from Baseline in endoscopic nasal polyp score (NPS) at Week 24 and average daily nasal congestion score (NCS). Endoscopic NPS and average daily NCS at Week 24 will be summarized by treatment group in terms of absolute values and changes from baseline.

4.11.2.1 Endoscopic Nasal Polyp Score (NPS)

Nasal Polyps 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 below:

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 interior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

The effect of treatment in terms of the change from Baseline to Week 24 in endoscopic NPS will be analyzed using Mixed-effect Model for Repeated Measures (MMRM).

The model will include treatment, presence of comorbid asthma, visit, treatment-by-visit interaction as categorical covariates, and endoscopic NPS at baseline as continuous covariates. Patient will be included as a random effect. An unstructured (UN) covariance matrix will be used to model the within-subject correlation. If this model fails to converge, then Akaike's Information Criterion (AIC) will be used to select the best covariance matrix among compound symmetry (CS), first-order autoregressive (AR(1)), and Toeplitz (TOEP). The treatment effect will be estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups will be also presented.

The sample SAS code for MMRM:

```
proc mixed data= data;
    class subjid cmabl trt01pn(ref='1') avisitn;
    model chg = trt01pn cmabl trt01pn*avisitn npsbl*avisitn / ddfm=kr;
    repeated avisitn / subject=subjid type=UN;
    lsmeans trt01pn*avisit / pdiff cl alpha=0.05;
    ods output lsmeans=lsmeans diffs=diffs;
run;
```

A plot showing the LS mean of endoscopic NPS ± SE bar over time within each treatment group will be provided.

Sensitivity analyses to investigate the impact of the choice of method for handling missing data and the choice of analysis set will be performed as described in 4.11.3.

By-subject listing of the primary efficacy data will also be provided.

4.11.2.2 Average Daily Nasal Congestion Score (NCS)

Daily Nasal Congestion Score (NCS) will be assessed by the patient through a patient diary from Visit 1 throughout the study by using a 0 to 3 categorical scale for severity of symptoms from none to severe over the past 24 hours.

Question: How would you rate nasal congestion over the last 24 hours?	
0	None
1	Minor
2	Moderate
3	Severe

Weekly mean of daily nasal congestion score will be calculated as sum of non-missing daily nasal congestion score divided by number of days with non-missing daily nasal congestion score using analysis window (Table). The effect of treatment in terms of the change from Baseline week (i.e. average of 7 days prior to the baseline visit) to Week 24 (i.e. average of 7 days prior to the Week 24 visit) in average daily NCS will be also analyzed using Mixed-effect Model for Repeated Measures (MMRM).

The model will include treatment, presence of comorbid asthma, visit, treatment-by-visit interaction as categorical covariates, and average daily NCS at baseline as continuous covariates. Patient will be included as a random effect. An unstructured (UN) covariance matrix will be used to model the within-subject correlation. If this model fails to converge, then Akaike's Information Criterion (AIC) will be used to select the best covariance matrix among compound symmetry (CS), first-order autoregressive (AR(1)), and Toeplitz (TOEP). The treatment effect will be estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups will be also presented.

The sample SAS code for MMRM:

```
proc mixed data= data;
    class subjid cmabl trt01pn(ref='1') avisitn;
    model chg = trt01pn cmabl trt01pn*avisitn ncsbl*avisitn / ddfm=kr;
    repeated avisitn / subject=subjid type=UN;
    lsmeans trt01pn*avisit / pdiff cl alpha=0.05;
    ods output lsmeans=lsmeans diffs=diffs;
run;
```

In addition to primary efficacy analysis summary, weekly mean of daily nasal congestion score will be summarized using descriptive statistics by treatment and overall.

A plot showing the LS mean of average daily NCS ± SE bar over time within each treatment group will be provided.

Sensitivity analyses to investigate the impact of the choice of method for handling missing data and the choice of analysis set will be performed as described in 4.11.3.

By-subject listing of the primary efficacy data will also be provided.

4.11.3 Sensitivity Analysis

4.11.3.1 Sensitivity Analysis using PMM-MI

To assess the robustness of the study conclusions to the choice of imputation method, the sensitivity analyses will be performed for the primary variable using control-based Pattern Mixture Model Multiple Imputation (PMM-MI) under the missing not at random (MNAR) assumption, which assumes the missingness depends on the unobserved study data and cannot be predicted solely based on subject's observed data.

Control-based PMM-MI under MNAR involves following standard steps. Same procedures will be followed for average daily NCS.

Step 1. Assessing the pattern of missing data

To investigate the pattern of missing data, 'ods output misspattern' will be used in the MI procedure of the SAS system (PROC MI). The imputation method will be based on the observed pattern of

missing data and amount of missing data. The pattern of missing data will be assessed as monotone or arbitrary.

```
proc mi data=non_mono seed=xxx nimpute=0;
    var trt01pn cmabl y0-y13; *y0=baseline, y13=week24;
    ods output misspattern=pattern;
run;
```

Step 1-a. Turning the arbitrary missing patterns to monotone missing patterns under MAR assumption

If a mixture of non-monotone and monotone missing patterns exist in the data with majority of monotone missing patterns, then the arbitrary missing patterns will be converted to monotone missing patterns under MAR assumption.

```
proc mi data=non_mono out=mono seed=xxx nimpute=m;
    min=. . x x x x x x x x x x x x x; *period (.) means no imputation needed;
    max=. . y y y y y y y y y y y y y;
    var trt01pn cmabl y0 y1 y2 y3 y4 y5 y6 y7 y8 y9 y10 y11 y12 y13;
    mcmc chain=multiple impute=monotone;
run;
```

Step 2. Generation of imputed datasets using control-based pattern imputation

PROC MI will be used to generate *m* complete datasets. The selection of *m* depends on the required computing time but has been recommended varying from 5 to 100.

```
proc mi data=mono seed=xxx nimpute=m outs=imputed;
    min=. . x x x x x x x x x x x x x;
    max=. . y y y y y y y y y y y y y;
    by _imputation_;
    class trt01pn cmabl;
    var cmabl y0 y1 y2 y3 y4 y5 y6 y7 y8 y9 y10 y11 y12 y13;
    monotone reg(/details);
    mnar model(y1 y2 y3 y4 y5 y6 y7 y8 y9 y10 y11 y12 y13/ modelobs=(trt01pn='1')); *only
control group is used to derive the imputation model;
run;
```

Step 2-a. Convert datasets into long format in which CHG variable represents all change from baseline with different values of avisit.

Step 3. Conducting model-based analysis using each imputed dataset

The *m* complete datasets are analyzed using MMRM.

```
proc mixed data= imputed;
    by _imputation_;
    class subjid cmabl trt01pn(ref='1') avisitn;
    model chg = trt01pn cmabl trt01pn*avisitn ncsbl*avisitn / ddfm=kr;
    repeated avisitn / subject=subjid type=UN;
    lsmeans trt01pn*avisit / pdiff cl alpha=0.05;
    ods output lsmeans=lsmeans diffs=diffs;
run;
```

Step 4. Pooling the results from the imputed *m* datasets for inference

The results from the m complete datasets are combined to produce inferential results.

```
proc sort data=lsmeans;
    by trt01pn avisitn _imputation_;
run;

proc mianalyze parms=lsmeans;
    modeleffects trt01pn*avisitn;
    ods output ParameterEstimates=lsm;
run;

proc sort data=diffs;
    by avisit _imputation_;
run;

proc mianalyze parms=diffs;
    modeleffects trt01pn*avisitn;
    ods output ParameterEstimates=dif;
run;
```

The Per Protocol Set analyses will be performed using the same imputation method as for the Full Analysis Set analyses.

4.11.3.2 Sensitivity Analysis for Use of Rescue Medication

To assess the robustness of the study conclusions to use of rescue medication, another sensitivity analysis will be performed on the primary variable based on FAS.

Rescue medications are defined as below and will be reviewed by Parexel Medical Monitor:

- Nasal lavage with saline and/or systemic antibiotics (up to 2 weeks in case of acute infection)
- Short course oral CS (prednisone or prednisolone); use of oral/systemic CS for ≤ 5 consecutive days
- Treatment with oral/systemic steroids for > 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.*

If patients used any rescue medication before Week 24, their assessments after the first use of rescue medication will be set to missing, and missing values at week 24 will be imputed using the subject's worst observed value over all previous time points including baseline value. Then the primary efficacy analysis using MMRM will be performed.

4.11.4 Secondary Efficacy Analyses

The similar analyses to primary analysis will be applied to following secondary endpoints:

- Percentage of maxillary sinus volume occupied by disease on CT and Lund-Mackay Computed Tomography scores from patients enrolled at Study Centers that are approved and qualified to perform CT scans

- University of Pennsylvania Smell Identification Test (UPSIT)
- Visual Analogue Scale for Rhinosinusitis (VAS-RS) [Appendix]
- Total Nasal Symptom Score (TNSS) [Appendix B – Total Nasal Symptom Score (TNSS)]
- 22-item Sinonasal Outcome Test (SNOT-22) [Appendix C – Sino-Nasal Outcome Test-22 QUESTIONNAIRE (SNOT-22)]
- Average daily anterior rhinorrhea score (from diary) *
- Average daily posterior rhinorrhea score (from diary) *
- Average daily loss of smell score (from diary) *
- Daily subject-assessed Nasal Peak Inspiratory Flow (NPIF) *

*Weekly mean will be calculated as sum of non-missing endpoint divided by number of days with non-missing endpoint for daily assessments listed using analysis window (Table). The effect of treatment in terms of the change from Baseline week (i.e. average of 7 days prior to the baseline visit) to Week 24 (i.e. average of 7 days prior to the Week 24 visit) will also be analyzed using MMRM.

Time to first rescue treatment (systemic corticosteroid for > 5 consecutive days) or having had surgery for nasal polyps during the 24-week Treatment Period will be analyzed using a Cox proportional hazard model. The model will be adjusted by treatment, presence of comorbid asthma, endoscopic NPS at Baseline, and average daily NCS at Baseline. Subjects who do not experience rescue treatment or surgery for nasal polyps during the 24-week Treatment Period will be censored at the earliest day among the component censoring times (end of study date, premature study discontinuation date, lost to follow-up date, date of death). Any events after 24-week Treatment Period will not be counted.

Estimated adjusted hazard ratios will be summarized with associated 95% CI and p-values.

The sample SAS code for the Cox proportional hazards model:

```
proc phreg data=datain;
    class subjid cmabl trt01pn(ref='1');
    model avisitn*event (1) = trt01pn cmabl / ties=efron rl=wald type3(wald);
        *0 is event, 1 is censored*;
    assess var = (trt01pn cmabl) ph / resample;
        *testing the proportionality assumption. Resample is specified to request the supreme tests
    of the null hypothesis that proportional hazards hold*;
    hazardratio trt01pn / diff=ref cl=wald alpha=0.05;
    ods output hazardratios=hazard;
run;
```

Time to first rescue treatment or having had surgery for nasal polyps during the 24-week Treatment Period will be displayed graphically for each treatment group using a Kaplan-Meier curve and analyzed using a log-rank test to compare the curved between the treatment groups.

The sample SAS code for the Kaplan-Meier Curve:

```
proc lifetest data=datain atrisk plots=survival (atrisk cb) outs=dataout;
    class subjid cmabl trt01pn(ref='1');
    time avisitn*event (1) = trt01pn cmabl;
run;
```

Proportion of subjects requiring rescue treatment (systemic corticosteroid for > 5 consecutive days) or surgery for nasal polyps during the 24-week Treatment Period will be calculated with the corresponding 95% CI by treatment group. Clopper-Pearson interval will used to calculate the exact confidence interval for binomial proportion. The difference between each CBP-201 group and placebo group and the corresponding 95% CI will be calculated as well. Cochran–Mantel–Haenszel (CMH) test stratified by presence of comorbid asthma will be performed and odds ratio will be provided with 95% confidence interval.

The sample SAS code for CMH test:

```
proc freq data=data order=data;
    table trt01pn*rescuetrt*cmabl / relrisk cmh;
run;
```

4.11.5 Exploratory Efficacy Analysis

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 FEV_1 for subjects with asthma
- 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)

Weekly mean of daily nasal congestion score will be calculated as sum of non-missing daily nasal congestion score divided by number of days with non-missing daily nasal congestion score using analysis window (Table).

Proportion of subjects with minimal clinically important difference ≥ 8.9 in SNOT-22 at Week 24 will be calculated with the corresponding 95% CI by treatment group. Clopper-Pearson interval will used to calculate the exact confidence interval for binomial proportion. The difference between each CBP-201 group and placebo group and the corresponding 95% CI will be calculated as well. Cochran–Mantel–Haenszel (CMH) test stratified by presence of comorbid asthma will be performed and odds ratio will be provided with 95% confidence interval.

The sample SAS code for CMH test:

```
proc freq data=data order=data;
    table trt01pn*snot*cmabl / relrisk cmh;
run;
```

Healthcare resource utilization at each visit up to Week 24 will be summarized using descriptive statistics by treatment and overall, as described in 4.13.4.

By-subject listings of each exploratory efficacy endpoint will also be provided.

4.12 Safety Evaluation

4.12.1 Extent of Exposure

Duration of treatment (see 4.2 for definition), cumulative amount of study drug administered during treatment period, and number of injection interruption will be summarized on Safety Set by treatment and overall. By-subject listing of extent of exposure will also be provided.

4.12.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. Severity and causality of AE will be evaluated by the investigator. Severity of AE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Incomplete start and end date of the AE will be imputed as described in **Error! Reference source not found.**.

Subjects with multiple incidents of events for a given preferred term (PT) and system organ class (SOC) will be counted only once. Similarly, if a subject experiences multiple incident of events for a given PT and SOC, the worst severity will be used in the summaries presenting severity, and the worst causality to study drug will be used in the summaries presenting causality, respectively.

Any missing severity will be queried for completion. If the severity is still missing in the final data and the outcome of AE is death, then it will be deemed as Grade 5, and if the life-threatening is marked, then it will be deemed as Grade 4. Otherwise, the severity still missing in the final data will be deemed as Grade 3.

Any missing causality will also be queried for completion, and any events that still have missing causality in the final data will be deemed as 'Related'.

The imputed severity and relationship will be used in table summary, but the original value will be maintained as missing in the by-subject listing.

Adverse event summaries will be sorted in terms of decreasing frequency for SOC, and PT within SOC, in the overall group, and then alphabetically for SOC, and PT within SOC if there are any ties in frequency.

An overall summary of AEs will include the number and percentage of subjects in the following categories:

- Any AEs
- AEs by maximum severity
- Any AEs related to study drug
- Any AEs related to study procedure
- Any AEs occurring more than 5% of subjects in overall
- Any serious AEs
- Any AEs leading to death
- Any AEs leading to study drug discontinuation
- Any AEs leading to study drug interruption
- Any TEAEs
- TEAEs by maximum severity
- Any TEAEs related to study drug
- Any TEAEs related to study procedure
- Any TEAEs occurring more than 5% of subjects in overall
- Any serious TEAEs

- Any TEAEs leading to death
- Any TEAEs leading to study drug discontinuation
- Any TEAEs leading to study drug interruption

Summaries of following AEs including the number and percentage of subjects will also be provided:

- AEs by SOC and PT
- Serious AEs by SOC and PT
- TEAEs by SOC and PT
- TEAEs by SOC and PT for Subjects with Rescue Medications
- TEAEs by decreasing frequency of PT
- TEAEs by SOC, PT, and maximum severity
- TEAEs of grade 3 or higher by SOC and PT
- TEAEs related to study drug by SOC and PT
- TEAEs related to study procedure by SOC and PT
- Any TEAEs occurring more than 5% of subjects in overall
- Serious TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study drug interruption by SOC and PT

By-subject listings of corresponding adverse events summary will also be provided.

4.12.3 Adverse Event of Special Interest

The TEAEs of special interests are defined as:

- Conjunctivitis
- Keratitis
- Anaphylaxis
- Parasitic and opportunistic infections
- Pregnancy
- Symptomatic overdose
- Injection site reactions lasting longer than 24 hours
- AST/ALT elevated > 5X ULN

The TEAEs of special interests will be summarized using frequencies and percentages by SOC and PT. Further analysis on AESI will also be summarized including the risk difference, its 95% confidence interval, and p-value using CMH test stratified by presence of comorbid asthma if there are at least 4 subjects in any treatment arm. The risk difference will be computed as each CBP-201 treatment group versus placebo. The confidence intervals and p-values will not be adjusted for

multiplicity so should be considered accordingly. By-subject listings will also be provided for all AESIs.

4.12.4 Clinical Laboratory Evaluation

All laboratory values will be reported and summarized using standard international (SI) units (Appendix D – *Laboratory SI U*). CTCAE v5.0 will be used for the laboratory toxicity grade (Appendix E*: CTCAE V5.0 Toxicity Grading for Laboratory Parameters*).

The following central laboratory tests will be summarized:

- Hematology: red blood cell count, hemoglobin level, hematocrit level, white blood cell count with differential, and platelet count
- Serum Chemistry: blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin, sodium, potassium, calcium, chloride, bicarbonate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), creatine phosphokinase (CPK), albumin, total protein, total cholesterol, triglycerides, C-reactive protein (CRP), and glucose
- Urinalysis: pH, protein, glucose, ketones, bilirubin, blood (hemoglobin), urobilinogen, nitrites, leukocytes, and specific gravity; microscopic analysis if abnormal

Continuous test results for each parameter and changes from baseline will be summarized at each visit by treatment and overall using descriptive statistics. Categorical test results for each parameter will be summarized at each visit by treatment and overall using frequencies and percentages. Shift of laboratory toxicity grade from baseline to each post-baseline visit will be summarized by treatment and overall. By-subject listings of laboratory parameters will also be provided.

Laboratory values will be listed by subject and study time point including changes from baseline, where available. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

4.12.5 Vital Signs

Descriptive summaries of actual values and changes from baseline at each visit will be summarized for temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate by treatment and overall. Baseline of vital signs is defined as pre-dose at Baseline visit. By-subject listing of vital sign parameters will also be provided.

4.12.6 Electrocardiograms

Descriptive summaries of actual values and changes from baseline at each visit will be summarized for the electrocardiogram parameters by treatment and overall. A separate summary of abnormal findings will be provided using frequencies and percentages. By-subject listing of electrocardiogram parameters will also be provided.

4.12.7 Physical Examinations

A complete or brief physical examinations will be conducted at Screening; Baseline; Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28 during treatment period; Week 28 and End of Study visit during follow-up period.

A complete physical examination will be conducted at Screening and End of Study visit, and includes:

- General appearance
- Head, eyes, ears, nose, and throat (HEENT)
- Neck
- Thyroid
- Skin
- Cardiovascular system
- Respiratory system
- Lymph nodes
- Musculoskeletal system
- Abdomen
- Fundoscopy (if available)
- Nervous system
- Extremities

A brief physical examination will be in all other visits and includes:

- General appearance
- Eyeball
- Lungs
- Lymph nodes

Abnormal findings of physical examinations will be summarized at each visit using frequencies and percentages by treatment and overall. By-subject listing of all physical examination parameters will also be provided.

4.12.8 Data and Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be set up periodically to review and evaluate all tolerability, descriptive primary efficacy data, and safety data for subject safety, study conduct and progress, and to make recommendations to the sponsor concerning the continuation, modification, or termination of the trial. The DSMB will be comprised of relevant clinical experts, drug safety and benefit-risk assessment experts, clinical trial methodology experts, and an independent DSMB biostatistician. These members will not be directly involved in the conduct of the study. Each meeting will be consisted of open and closed session. Unblinded information will be only reviewed during the closed session to maintain blinding and to prevent potential bias. The meeting minutes containing unblinded information will be marked as “Confidential” and distributed to the members of the DSMB only.

A separate DSMB Charter document will outline further details about the DSMB responsibilities and authorities, schedule of data review, define the board process, communications, meeting format, data access, and the lists of the reports.

4.13 Other Analyses

4.13.1 Pharmacokinetics

Whole blood for plasma CBP-201 concentrations will be collected, and additional sampling will be obtained after the last treatment dose to characterize the return to Baseline, as noted in the schedule of assessment. The individual and treatment group steady-state trough pharmacokinetic (PK) profile will be calculated for PK analysis.
The details of PK analysis will be provided in a separate PK analysis plan.

4.13.2 Pharmacodynamics

Pharmacodynamic (PD) blood samples for biomarkers of inflammation include peripheral eosinophil counts, Eotaxin-3, eosinophil cationic protein (ECP), total immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC), and periostin. Blood eosinophil count will be measured as part of hematology test and included in hematology summary. CRP will be determined as part of the serum chemistry and included in serum chemistry summary. Absolute analysis value and change from baseline of peripheral eosinophil counts, Eotaxin-3, eosinophil cationic protein (ECP), total immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC), and periostin to each visit will be summarized by treatment using descriptive statistics on PK Set. By-subject listing will also be provided.

4.13.3 Immunogenicity

The immunogenicity of CBP-201 with prolonged use will be determined with the collection of blood samples for measurement of anti CBP-201 antibodies (ADA) throughout the study. Further, neutralizing activity of neutralizing antibodies (NAb) will be measured on samples that test positive for anti CBP-201 antibodies. Absolute analysis value and change from baseline of ADA and NAb blood sample will be summarized by treatment using descriptive statistics on PK Set. By-subject listing will also be provided.

4.13.4 Health Economics

The following data will be collected during the study in health care utilization eCRF:

- Number of visits (in-person or telehealth) to usual healthcare provider for nasal polyps since last visit
- Number of urgent care admissions for nasal polyps since last visit
- Number of emergency room admissions for nasal polyps since last visit
- Number of days on hospitalization for nasal polyps since last visit
- Incident of surgery for nasal polyps since last visit

Each question at each visit will be summarized by treatment and overall using descriptive statistics. By-subject listing of health care utilization will also be provided.

4.14 Determination of Sample Size

The sample size of the study is determined 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.

4.15 Changes in the Conduct of the Study or Planned Analysis

Enrollment of Sponsor's Phase 2 trial evaluating CBP-201 in chronic rhinosinusitis with nasal polyps, which commenced in June 2021, has faced challenges due to the macroenvironment -- namely ongoing impact of COVID and the current Russia-Ukraine conflict throughout [Eastern] Europe.

Therefore, the Sponsor has made the decision to terminate this trial early, and the planned analyses have been changed to focus on safety assessments.

For the efficacy endpoints, only descriptive summary statistics will be provided for the co-primary efficacy assessments. No formal hypotheses will be tested due to the small sample size. No sensitivity or subgroup analyses will be performed. All other efficacy assessments will be listed except percentage of maxillary sinus volume occupied by disease on CT and Lund-Mackay Computed Tomography scores.

5 REFERENCES

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.

Ratitch, Bohdana, and Michael O'Kelly. "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures." PharmaSUG2011, 2011, www.lexjansen.com/pharmasug/2011/SP/PharmaSUG-2011-SP04.pdf.

SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©2013. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

"The MI Procedure". SAS® 9.4 and SAS® Viya® 3.4 Programming Documentation. SAS Institute Inc., 2019, https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_mi_details61.htm.

Suzhou Connect Biopharmaceuticals, Ltd., "CLINICAL STUDY PROTOCOL CBP-201-WW003: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate CBP-201 in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps" 2021.

6 APPENDICES

6.1 Appendix A – Visual Analogue Scale for Rhinosinusitis (VAS-RS)

Seriousness of the complaints: Please draw a vertical line to the point that best corresponds to, how bothersome were the following symptoms within the last month, as given to the example:

* Example None More than I can imagine

|_____|

* Total sinus symptoms:

None More than I can imagine

|_____|

* Nasal blockage: None More than I can imagine

|_____|

* Headache /pressure on the face:

None More than I can imagine

|_____|

* Loss of smell: None More than I can imagine

|_____|

* Post-nasal drip (secretions from the nose down to the throat):

None More than I can imagine

|_____|

* Runny nose: None More than I can imagine

|_____|

* Itchy eyes: None More than I can imagine

|_____|

* Itchy nose: None More than I can imagine

|_____|

* Sneezing: None More than I can imagine

|_____|

* Tearing: None More than I can imagine

|_____|

* Cough: None More than I can imagine

|_____|

* Tightness/pressing sensation on the chest:

None More than I can imagine

|_____|

* Shortness of breath/difficulty with breathing:

None More than I can imagine

|_____|

* Wheezing:

None More than I can imagine

|_____|

6.2 Appendix B – Total Nasal Symptom Score (TNSS)

Total Nasal Symptom Scores (TNSS) is the total of 4 related symptoms. Each symptom (sneezing, congestion, itching, and rhinorrhea) is graded from 0 to 3 by the patients.

Score	Description	Symptoms
0	None	No symptoms evident
1	Mild	Symptom present but easily tolerated
2	Moderate	Definite awareness of symptom; bothersome but tolerable
3	Severe	Symptom hard to tolerate; interferes with daily activity

The nasal symptoms are then added together for each symptom to get the total TNSS.

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

Figure S1: Sino-Nasal Outcome Test-22 Questionnaire

A: Considering how severe the problem is when you experience it and how frequently 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**	
1. Need to blow nose	0	1	2	3	4	5	
2. Sneezing	0	1	2	3	4	5	
3. Runny nose	0	1	2	3	4	5	
4. Cough	0	1	2	3	4	5	
5. Post nasal discharge (dripping at the back of your nose)	0	1	2	3	4	5	
6. Thick nasal discharge	0	1	2	3	4	5	
7. Ear fullness	0	1	2	3	4	5	
8. Dizziness	0	1	2	3	4	5	
9. Ear pain	0	1	2	3	4	5	
10. Facial pain/pressure	0	1	2	3	4	5	
11. Difficulty falling asleep	0	1	2	3	4	5	
12. Waking up at night	0	1	2	3	4	5	
13. Lack of a good night's sleep	0	1	2	3	4	5	
14. Waking up tired	0	1	2	3	4	5	
15. Fatigue	0	1	2	3	4	5	
16. Reduced productivity	0	1	2	3	4	5	
17. Reduced concentration	0	1	2	3	4	5	
18. Frustrated/restless/ irritable	0	1	2	3	4	5	
19. Sad	0	1	2	3	4	5	
20. Embarrassed	0	1	2	3	4	5	
21. Sense of taste/smell	0	1	2	3	4	5	
22. Blockage/congestion of nose	0	1	2	3	4	5	

TOTAL: _____ _____ _____ _____ _____

GRAND TOTAL:

6.4 Appendix D – Laboratory SI Units

Panel	Parameter	SI Unit
Hematology	Eosinophil Count	10^9/L
	Hematocrit	Proportion of 1.0
	Hemoglobin	g/L
	Platelet Count	10^9/L
	Red Blood Cell (RBC) Count	10^12/L
	White Blood Cell (WBC) Count with Differential	%
Serum Chemistry	Alanine Aminotransferase (ALT)	U/L
	Albumin	g/L
	Alkaline Phosphatase (ALP)	U/L
	Aspartate Aminotransferase (AST)	U/L
	Blood Urea Nitrogen (BUN)	mmol/L
	Calcium	mmol/L
	Bicarbonate	mmol/L
	Chloride	mmol/L
	Creatinine	µmol/L
	Creatine Phosphokinase (CPK)	U/L
	C-Reactive Protein (CRP)	mg/L
	Gamma-Glutamyltransferase (GGT)	U/L
	Glucose	mmol/L
	Lactate Dehydrogenase (LDH)	U/L
	Potassium	mmol/L
	Sodium	mmol/L
	Total Bilirubin	µmol/L
	Total Cholesterol	mmol/L
	Total Protein	g/L
	Triglycerides	mmol/L
	Uric Acid	mmol/L
Urinalysis	Bilirubin	NA
	Hemoglobin	NA
	Glucose	NA
	Ketones	NA
	Leukocytes	NA
	Nitrites	NA
	pH	NA

Protein	NA
Specific Gravity	NA
Urobilinogen	NA
Microscopic Analysis if abnormal	NA

6.5 Appendix E: CTCAE V5.0 Toxicity Grading for Laboratory Parameters

CTCAE v5.0 SOC	CTCAE v5.0 Term	Laboratory Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	
	Eosinophilia	Eosinophils in the blood	>ULN and >Baseline	-		-
	Leukocytosis	White blood cells in the blood	-	-	>100,000/mm3	
Investigations	Activated partial thromboplastin time prolonged	Partial Thromboplastin Time (PTT)	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-
	Alanine aminotransferase increased	Alanine aminotransferase (ALT or SGPT) in the blood specimen	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Alkaline phosphatase increased	Alkaline phosphatase in a blood specimen	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

	Aspartate aminotransferase increased	Aspartate aminotransferase (AST or SGOT) in a blood specimen	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Blood bicarbonate decreased	Bicarbonate in a venous blood specimen	<LLN and no intervention initiated	-	-	-
	Blood bilirubin increased	Bilirubin in a blood specimen	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
	Blood lactate dehydrogenase increased	Lactate dehydrogenase in the blood specimen	>ULN	-	-	-
	Cholesterol high	Cholesterol in a blood specimen	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
	CPK increased	Creatine phosphokinase in a blood specimen	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
	Creatinine increased	Creatinine in a biological specimen	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

	GGT increased	Gamma-glutamyltransferase in the blood specimen	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Hemoglobin increased	Hemoglobin	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-
	INR increased	INR	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-
	Lipase increased	Lipase in a biological specimen	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms
	Lymphocyte count decreased	Lymphocytes in a blood specimen	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
	Lymphocyte count increased	Lymphocytes in the blood	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-
	Neutrophil count decreased	Neutrophils in a blood specimen	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L

	Pancreatic enzymes decreased	Pancreatic enzymes in a biological specimen	<LLN and asymptomatic			
	Platelet count decreased	Platelets in a blood specimen	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
	Serum amylase increased	Amylase in a serum specimen	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms
	White blood cell decreased	White blood cells in a blood specimen	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Metabolism and nutrition disorders	Acidosis	Acidity of the blood	pH <normal, but >=7.3	-	pH <7.3	
	Alkalosis	Alkalinity of the blood	pH >normal, but <=7.5	-	pH >7.5	
	Hypercalcemia	Calcium (corrected for albumin) in blood	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences

	Hyperkalemia	Potassium in the blood	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
	Hypermagnesemia	Magnesium in the blood	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
	Hypernatremia	Sodium in the blood	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
	Hypertriglyceridemia	Triglyceride concentration in the blood	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
	Hyperuricemia	Uric acid	>ULN without physiologic consequences	-	>ULN with physiologic consequences	
	Hypoalbuminemia	Albumin in the blood	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
	Hypocalcemia	Calcium (corrected for albumin) in the blood	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences

	Hypoglycemia	Glucose in the blood	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; lifethreatening consequences; seizures
	Hypokalemia	Potassium in the blood	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
	Hypomagnesemia	Magnesium in the blood	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences
	Hyponatremia	Sodium in the blood	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences
Renal and urinary disorders	Chronic kidney disease	eGFR or CrCl or Urine protein	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated

			protein/creatinine >0.5			
	Proteinuria	Urine protein	1+ proteinuria; urinary protein ≥ULN -	2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs	Urinary protein >=3.5 g/24 hrs; 4+ proteinuria	-

Signature Page for VV-TMF-1764580 v1.0

Reason for signing: Approved	Name: Amy Kim Role: Biostatistics Date of signature: 20-Jun-2022 14:12:26 GMT+0000

Reason for signing: Approved	Name: Yun Jang Role: Biostatistics Date of signature: 20-Jun-2022 14:16:00 GMT+0000

Reason for signing: Approved	Name: Daniel Miconi Role: Sponsor Date of signature: 20-Jun-2022 16:04:14 GMT+0000

Signature Page for VV-TMF-1764580 v1.0