Statistical Analysis Plan for Interventional Studies

Text Only

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Sponsor Name: Upstream Bio, Inc.

Protocol Number: UPB-CP-03

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Verekitug (UPB-101) in Participants with Chronic Rhinosinusitis with Nasal Polyps on a Background of Nasal Corticosteroids (VIBRANT)

Protocol Version and Date: (DD-Mmm-YYYY): V2.0; 09-Jul-2024

Syneos Health Project Code: 7044697

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Notice of Confidential and Proprietary Information:

Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**
1.0	12-Aug-2025	[redacted]	Initial Release Version
2.0	15-Aug-2025	[redacted]	Section 12 was updated to specify the data handling of values outside the range of the assay.

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
[redacted]	[redacted]	15-Aug-2025
[redacted]	[redacted]	15-Aug-2025
[redacted]	[redacted]	15-Aug-2025

Upstream Bio, Inc. Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
[redacted]	[redacted]	15-Aug-2025

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1. Glossary of Abbreviations

Abbreviation	Description
ACQ-6	Asthma Control Questionnaire-6
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALQ	Above Limit of Quantification
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below Level of Quantification
BSSRE	Blinded sample size re-estimation
CAS	Comorbid Asthma Set
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DMC	Data monitoring committee
DSS	Difficulty with Sense of Smell
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FEV1	Forced expiratory volume in 1 second
IAS	Immunogenicity Analysis Set
ICE	Intercurrent event
ICF	Informed Consent Form
IgE	Immunoglobulin E

Abbreviation	Description
ISR	Injection site reaction
ITT	Intention to Treat
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LMK	Lund Mackay
LSM	Least square means
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing Not at Random
MFNS	Mometasone furoate nasal spray
N/A	Not Applicable
NAb	Neutralizing antibody
NBS	Nasal Blockage Score
NCS	Nasal congestion score
NP(s)	Nasal polyp(s)
NPS	Nasal polyp score
NPSD	Nasal polyposis symptom diary
NSAID-ERD	Non-steroidal anti-inflammatory drug-exacerbated respiratory disease
PD	Pharmacodynamic(s)
PDAS	Pharmacodynamic Analysis Set
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Preferred Term
Q12W	Every 12 weeks
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

Abbreviation	Description
SC	Subcutaneous
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure, and Listing
TSS	Total symptom score
ULN	Upper Limit Normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WOCF	Worst Observation Carried Forward

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings. The Syneos Health Pharmacometrics group will assist with the pharmacokinetic (PK) analysis.

2.2. Timings of Analyses

Protocol Amendment 1 (dated 09 July 2024) introduced plan for two database locks (DBLs) instead of one originally planned DBL (Original Protocol dated 17 July 2023) for this study. With Amendment 1, the first DBL would be conducted after the last participant has reached Week 24, and the second and final DBL will be conducted after all participants complete their safety follow-up visits (EOS). Sponsor and the CRO analysis team planned to have appropriate blinded and unblinded teams to manage the two DBLs.

Due to a shorter than anticipated enrollment period, only one DBL will be conducted now; the DBL will occur after all participants complete their safety follow-up visits (EOS). The SAP will be finalized prior to the DBL.

Analysis after DBL will be performed after the completion of the following:

1. Agreement of the analysis populations based on the data review meeting (blinded data review meeting prior to the DBL).
2. Final vendor data has been sent to Syneos Health and reconciled by Data Management.
3. All required database cleaning activities have been completed and database lock has been declared by Data Management.
4. All criteria for unmasking the randomization codes have been met.
5. Randomization codes have been released to the statistics and programming team for programming and analysis.

Any post-hoc analyses completed to support planned study analyses which were not identified in this SAP will be documented and reported in appendices to the Clinical study report. Any results from these unplanned analyses (post-hoc) will also be clearly identified as such.

An interim analysis is also planned prior to completion of study enrollment based on blinded data. The purpose of the interim analysis is to evaluate sample size assumptions. The detail of the interim analysis is provided in Section 20.2.

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to assess the effect of verekitug (UPB-101) on endoscopic nasal polyp score (NPS) compared to placebo.

3.2. Secondary Objectives

The secondary objectives of this study are listed below:

- To assess the effect of verekitug (UPB-101) on nasal congestion score (NCS) compared to placebo
- To assess the effect of verekitug (UPB-101) on computed tomography (CT) scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)
- To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo
- To assess the effect of verekitug (UPB-101) on the need for treatment with systemic corticosteroids or nasal polyp (NP) surgery compared to placebo
- To assess the effect of verekitug (UPB-101) on total symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP) compared to placebo

3.3. Safety Objective

The safety objective of this study is to assess safety and tolerability of verekitug (UPB-101) compared to placebo.

3.4. Other Objectives

The other objectives of this study are listed below:

- To assess the effect of verekitug (UPB-101) on endoscopic NPS compared to placebo
- To assess the effect of verekitug (UPB-101) on NCS compared to placebo
- To assess the effect of verekitug (UPB-101) on loss of smell compared to placebo
- To assess the effect of verekitug (UPB-101) on total symptoms of CRSwNP compared to placebo
- To assess the effect of verekitug (UPB-101) on the resolution of NP compared to placebo
- To assess immunogenicity of verekitug (UPB-101)
- To assess the PK of verekitug (UPB-101)
- To assess the Pharmacodynamic (PD) effect of verekitug (UPB-101) on blood and nasal secretion biomarkers
- To assess the effect of verekitug (UPB-101) on adequacy of asthma control in participants with comorbid asthma
- To assess the effect of verekitug (UPB-101) on lung function in participants with comorbid asthma

- To assess the effect of verekitug (UPB 101) on CT scan opacification of the sinuses compared to placebo (CT scans not performed in Germany and Czechia)

4. Study Details/Design

4.1. Brief Description

This study is a Phase 2, randomized, double-blind, placebo-controlled, multinational, multi-center study to assess the efficacy and safety of verekitug (UPB-101) administered subcutaneously (SC) in participants with CRSwNP on background therapy with stable dosage of intranasal corticosteroids (INCS). This study consists of a 3 to 5-week Screening Period, a 24-week Treatment Period, and a 4-week Follow-up Period.

The purpose of this study is to evaluate the efficacy and safety of verekitug (UPB-101) in participants with CRSwNP on a background of nasal corticosteroids. Approximately 70 participants are planned for enrollment and will be randomized in 1:1 ratio to receive verekitug (UPB-101) or matching placebo. Background INCS will be standardized. The randomization will be stratified by the presence of comorbid asthma and/or non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), and prior NP surgery.

This study will consist of 2 treatment arms, verekitug (UPB-101) and placebo arms. Each participant will receive SC dose of verekitug (UPB-101) or placebo every 12 weeks (Q12W) for 24 weeks (i.e., 2 doses). Study intervention may be administered in the SC tissue of any extremity or on either side of the abdominal wall.

4.2. Participant Selection

The study population will consist of participants with CRSwNP. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

4.2.1. Inclusion Criteria

The inclusion criteria are described in Section 5.1 of the protocol.

4.2.2. Exclusion Criteria

The exclusion criteria are described in Section 5.2 of the protocol.

4.3. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.4. Treatment Assignment and Blinding

Medidata Randomization and Trial Supply Management (RTSM) will be used for participant and kit randomization.

After an up to 5-week screening period, eligible participants who continue to meet eligibility criteria at baseline will be centrally randomized 1:1 to one of the 2 arms of the study (verekitug [UPB-101] or placebo), according to the randomization schedule generated by the unblinded statistician. The randomization will be stratified by comorbid asthma and/or NSAID-ERD status (yes or no) and prior NP surgery (yes or no).

This is a double-blind study in which participants/care providers/Investigators/outcomes assessors, etc. are blinded to study intervention. Specific assessments and variables will also be blinded to preserve the blind. Since PK data and pharmacodynamic (PD) assessments from individual participants may be unblinded, such data will not be available to blinded parties. Therefore, until the entire study has been concluded and the database locked, results of eosinophil numbers, monocytes, basophils, immunoglobulin E (IgE), immunogenicity assessments, PK, and PD biomarkers as listed in Schedule of Assessment Table 1–1 from the protocol will be masked/blinded starting at Visit 2 Day 1 (Week 0) and will be accessible only to unblinded parties.

At the end of the study, the database lock will be declared after the completion of all procedures related to data cleaning, the medical review of the data, agreement of the final participant disposition, and agreement of the analysis populations upon blinded data review. Once database lock has been declared, the study will be unblinded and the individual treatment assignments as well as any unblinded data will be released to analyze the data.

Prior to database lock, unblinded data will be presented for data monitoring committee (DMC) meetings. A separate unblinded statistical team (statisticians and programmers) will conduct these analyses. Unblinded treatment assignments will be sent directly to the unblinded team from the RTSM lead. Any unblinded vendor data will be sent directly to the unblinded statistical team.

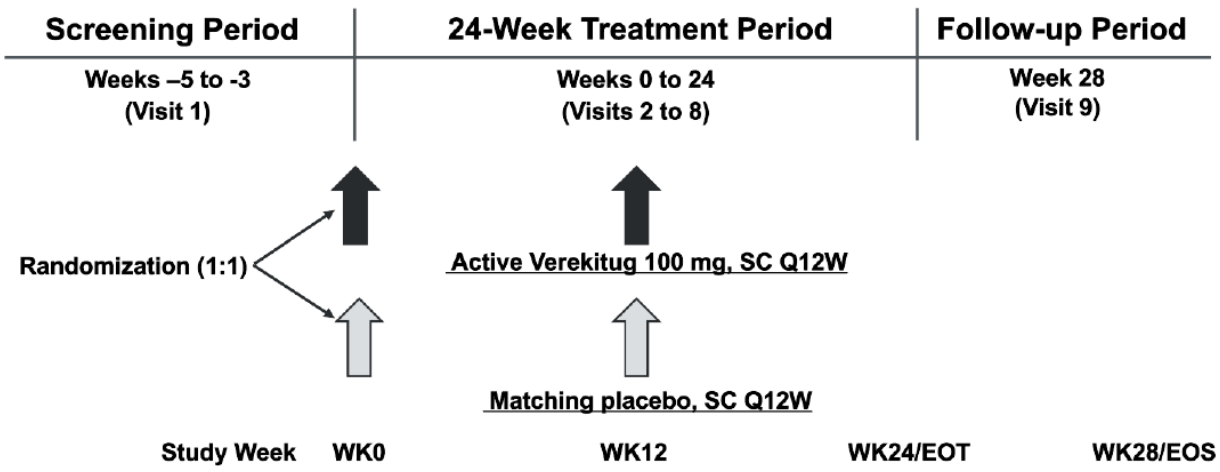
4.5. Administration of Study Medication

The administration of the study medication is described in section 6.1.1 of the protocol.

4.6. Study Procedures and Flowchart

The schedule of activities is presented in Section 1.3 table 1-1 of the protocol and in Appendix Section 20.1 of this SAP.

The study schema is presented below:



Note: The Screening Period includes at least 21 days of standardization of background INCS to MFNS or equivalent. The Follow-Up Period WK 28/EOS Visit will occur approximately 4 weeks after completion of the EOT and approximately 16 weeks after the last dose of study intervention.

EOT=End of Treatment, EOS=End of Study, MFNS=mometasone furoate nasal spray, Q12W=every 12 weeks, SC=subcutaneous, and WK=week.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline at Week 24 in NPS.

5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are listed below:

- Change from Baseline at Week 24 in the NCS evaluated by the nasal polyposis symptom diary (NPSD)
- Change from Baseline at Week 24 in opacification of sinuses measured by Lund Mackay (LMK) Score evaluated by quantitative CT assessment (CT scans not performed in Germany and Czechia)
- Change from Baseline at Week 24 in mean Difficulty with Sense of Smell (DSS) evaluated by the NPSD
- Proportion of participants requiring systemic corticosteroids or NP surgery
- Time to first nasal polyposis surgery and/or use of systemic corticosteroids for nasal polyposis up to Week 24
- Change from Baseline at Week 24 in NPSD total symptom score (TSS)

5.3. Pharmacokinetic Endpoints

The pharmacokinetic endpoint in this study is the summary of serum concentrations of verekitug (UPB-101) from Baseline, Treatment, and Follow-Up Periods.

5.4. Pharmacodynamic Endpoints

The pharmacodynamic endpoint in this study is the absolute and percent change from Baseline over Week 24 in blood and nasal secretion biomarkers.

5.5. Safety Endpoints

The safety endpoints in this study are adverse events (AEs), serious adverse events (SAEs), physical examinations, clinical laboratory assessments, vital signs, and electrocardiograms (ECGs) from Baseline over study duration, including the Follow-Up Period.

5.6. Other Endpoints

The other endpoints in this study are listed below:

- Change from Baseline over Week 24 in NPS
- Change from Baseline over Weeks 24 and 28 in NCS evaluated by the NPSD
- Change from Baseline over Weeks 24 and 28 in DSS evaluated by the NPSD
- Change from Baseline over Weeks 24 and 28 in NPSD TSS
- Proportion of participants at Week 24 who achieve a maximum NPS of 1 in each nostril
- Incidence of Antidrug antibodies (ADAs) during the study (including the post-treatment Follow-Up Period)
- In participants with ADAs, incidence of Neutralizing antibody (NAb) during the study (including the Follow-Up Period)
- Change from Baseline over Week 24 in participant ACQ-6 in participants with comorbid asthma
- Change from Baseline over Week 24 in FEV_1 in participants with comorbid asthma
- Change from baseline to Week 24 in three Dimensional CT volumetric measurement of the paranasal sinuses

5.7. Additional Endpoints

Additional endpoints which are based on existing efficacy assessments and support secondary and other efficacy endpoints include:

- Time to nasal polyposis surgery, systemic corticosteroids, and/or escalation of maintenance/background treatment for nasal polyposis up to Week 24
- Time to nasal polyposis surgery for nasal polyposis up to Week 24
- Time to systemic corticosteroids for nasal polyposis up to Week 24
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in bi-weekly NCS
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in bi-weekly DSS
- Proportion of Participants at Week 24 who Achieve >= 4 Point Decrease in bi-weekly TSS
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in bi-weekly Nasal Blockage Score (NBS)
- Proportion of Participants at Week 24 who Achieve a >= 1 Point Decrease in NPS
- Proportion of Participants at Week 24 who Achieve a >= 2 Point Decrease in NPS
- Proportion of Participants at Week 24 who Achieve a >= 5 Point Decrease in LMK score

- Change from Baseline over Weeks 24 and 28 in Sleep Score evaluated by the NPSD
- Change from Baseline over Weeks 24 and 28 in Daily Activities evaluated by the NPSD

6. Analysis Sets

The following analysis sets are defined in this study:

6.1. Screened Set

The Screened Set will include all participants who signed the informed consent form (ICF). Unless specified otherwise, this set will be used for participant disposition summaries and listings.

6.2. Intention to Treat Analysis Set

The Intent to Treat (ITT) Analysis Set will include all randomized participants. Participants will be analyzed according to the randomized treatment. The ITT Set will be used for all summary of demographic and baseline characteristics and analyses of efficacy endpoints.

6.3. Safety Analysis Set

The Safety Analysis Set (SAF) will include all participants who were administered at least one dose of study medication. Participants will be analyzed according to the treatment received. The SAF will be used for all analyses of safety endpoints.

6.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) will include all participants in the safety analysis set who received verekitug (UPB-101) and have at least one evaluable PK sample.

6.5. Pharmacodynamic Analysis Set

The PD Analysis Set (PDAS) will include all participants in the safety analysis set who received study treatment and have at least one evaluable PD sample.

6.6. Comorbid Asthma Set

The Comorbid Asthma Set (CAS) will include all participants in the ITT set who have comorbid asthma.

6.7. Immunogenicity Analysis Set

The immunogenicity analysis set (IAS) will include all participants in the safety analysis set and have at least one evaluable ADA sample.

6.8. Per Protocol Set

The Per Protocol Set (PPS) includes all participants in the ITT without any major protocol violations that could influence the validity of the data for the primary efficacy evaluation. All criteria to exclude participants from the PPS will be made and documented based on a blinded review of the data prior to the unblinding of the study. More specifically, participants who have received less than 2 doses of the cumulative planned study intervention (Verekitug or Placebo) or have received any of the following prohibited concomitant treatment or investigational treatment (preferred term) during the study will be excluded from the PPS:

- Dupilumab
- Mepolizumab

- Benralizumab
- Omalizumab
- Tezepelumab

7. Estimands

The primary estimand of interest is defined by the following attributes:

Attribute	**Specification**
Treatment condition	Condition of interest: randomized to UPB-101 Alternative condition: randomized to Placebo
Participant population	All randomized participants with CRSwNP as defined by study protocol eligibility criteria (ITT)
Variable	Change from baseline in NPS at Week 24
Intercurrent events (ICE)	The following ICEs are expected to happen during the study: • ICE 1: Treatment discontinuation • ICE 2: Use of rescue surgical treatment for CRSwNP • ICE 3: Use of rescue systemic corticosteroids for CRSwNP or for comorbid conditions • ICE 4: Escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP For ICE 1 and ICE 3, treatment policy strategy will be applied and observed NPS after study treatment discontinue will be used for analysis. For ICE 3, observed NPS after rescue systemic corticosteroids for CRSwNP or for comorbid conditions will be used for the analysis. For ICE 2 and ICE 4, composite variable strategy will be applied: NPS after the start of another treatment for CRSwNP will be replaced by worst possible value 8. ICE 2 will be identified as described in Section 9.5.1. ICE 3 will be identified as described in Section 9.4.3. ICE 4 will be identified as described in Section 9.4.4.
Population level summary	Mean difference between UPB-101 and Placebo treatment groups in the change from baseline at Week 24
Main estimator	Least square means (LSM) difference between UPB-101 and Placebo treatment groups at Week 24 as assessed by mixed model repeated measures (MMRM)

8. General Aspects for Statistical Analysis

8.1. General Methods

All analyses and summary outputs will be generated using SAS® version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to SYNH programming standards and SAS validation procedures. Summaries will be presented by study arm and overall unless otherwise specified.

Unless otherwise noted, continuous variables will be summarized using the number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), median, minimum, and maximum values as summary statistics. The minimum and maximum will be displayed to the precision with which the data were collected. The mean, median, and quartiles will be displayed to one additional decimal place and the SD will be displayed to two additional decimal places, where applicable. 95% confidence intervals (CIs) for the mean may additionally be presented in descriptive summaries where appropriate.

Descriptive statistics for categorical/qualitative data will include frequency counts and percent of participants in each group, where the denominator for percentages is the underlying analysis set, unless otherwise stated. All summaries will be presented by arm unless otherwise specified.

All relevant participant data will be included in listings.

8.2. Key Definitions

8.2.1. Study Day

The day of first dose of study drug is defined as Study Day 1.

Study day for an event or measurement occurring before the date of the first dose will be calculated as follows:

Study Day = (Event/Measurement Date – Date of First Dose)

Study day for an event or measurement occurring on the date of the first dose is study day 1. Study day for an event or measurement occurring on or after the date of the first dose will be calculated as follows:

Study Day = (Event/Measurement Date – Date of First Dose) +1

Study Day is not applicable for bi-weekly derived mean endpoints (NCS, DSS, TSS, NBS, Sleep score, and Daily Activities Score).

8.2.2. Baseline

Unless otherwise specified, the baseline value is defined as the last non-missing valid value prior to first administration of study drug (on Day 1). If an assessment is conducted on the day of first study drug administration and time of the assessment is unknown, the assessment will be assumed to have occurred prior to first administration of study drug. For ACQ-6, baseline will be defined as the last non-missing valid value on or prior to the date of first administration of study drug.

Baseline value for bi-weekly derived mean endpoints (NCS, DSS, TSS, NBS, Sleep score, and Daily Activities Score) is described in section 10.

For participants who were randomized but not dosed, baseline will be defined as the last non-missing valid value prior to randomization date and time. If an assessment is conducted on the day of randomization and time of the assessment is unknown, the assessment will be assumed to have occurred prior randomization. For ACQ-6, baseline will be defined as the last non-missing valid value on or prior to the date of randomization. For bi-weekly derived mean endpoints (NCS, CSS, TSS, NBS, Sleep score, and Daily Activities Score), the calculation will be relative to the randomization date instead of Study Day 1.

8.2.3. Change from Baseline

The change from baseline will be calculated for each post-baseline assessment as:

Change = post-baseline value – baseline value

Percent change = 100 * change / baseline value

8.3. Missing Data

Unless stated otherwise, missing data will not be imputed. When relevant, sections below will address how missing data will be handled for particular analyses.

For AEs with partial or completely missing start dates, start dates will be imputed for the purposes of determining whether the event occurred prior to or after first study drug administration based on the following:

- AE start dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the month and year of first dosing of study drug, in which case the date will be imputed using the date of first dosing of study drug and will be considered a treatment-emergent adverse event (TEAE).
- AE start dates with missing day and month will be assumed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the year of first dosing of the study drug, in which case the date will be imputed using the date of the first dosing of study drug and will be considered a TEAE.
- AE with completely missing start date will be imputed using the date of first dosing of study drug and will be considered a TEAE
- AE partial end dates will not be imputed.
- If the end date is before the first dosing date then impute start date as the first day of the non-missing year or non-missing month

Partial dates entered in the ‘Prior and Concomitant Medications’ form will be imputed for the purposes of determining whether the record is a concomitant or prior medication based on the following:

- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month.
- Medications that are not ongoing and have a medication stop date with missing day and month will be assumed to occur on the last day of the non-missing year (i.e., December 31).
- Medications that are not ongoing and have a medication with completely missing stop date will be considered as concomitant.

- Partial or missing start dates will be imputed following the same logic as described for partial or completely missing AE start dates.

In the listings, partial or missing dates will be reported as collected in the electronic data capture (EDC).

8.4. Visit Windows

Efficacy and safety endpoints will be analyzed according to the nominal visits unless otherwise specified. For participants who discontinued study treatment early but agree to remain in the study will have end of treatment (EOT) and end of study (EOS) assessments approximately 12 weeks and 16 weeks after the last dose of study intervention, respectively. For these participants, EOT assessments will map to Week 12 analysis visit if the EOT assessment was conducted within ±7 days of Study Day 84, except for nasal endoscopy and CT assessments. For nasal endoscopy, post-baseline assessments will be mapped to an analysis visit according to the actual study day based on the following analysis window:

Analysis Visit	Target Day	Analysis Window
Visit 6/Week 12	84	Day 70 – Day 98
Visit 8/Week 24	168	Day 140 – Day 196

If more than one assessment occured within the same visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with the later date will be used.

For CT, post-baseline assessments will be mapped to an analysis visit according to the actual study day based on the following analysis window:

Analysis Visit	Target Day	Analysis Window
Visit 8/Week 24	168	Day 140 – Day 196

If more than one assessment occured within the same visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with the later date will be used.

Data from unscheduled visits or EOS visits for participants who discontinue study treatment early will be included in data listings but in general, unscheduled or EOS data will be excluded from the summary tables by visits unless otherwise specified.

8.5. Pooling of Centers

The data from all centers will be pooled by region for analyses unless specified otherwise.

Region is defined as “USA and Western Europe” including USA, Germany, Spain and “Eastern Europe” including Czechia and Poland.

8.6. Subgroups

The primary efficacy endpoint data from subgroups of participants in the ITT will be analyzed as specified below. These analyses will be considered exploratory and will comprise of descriptive summaries and will not involve formal hypothesis testing.

Prespecified subgroup analyses will be conducted for:

- Eosinophil level (<150 cells/uL, ≥150 cells/uL)
- Eosinophil level (<300 cells/uL, ≥300 cells/uL)
- Presence of comorbid asthma and/or NSAID-ERD (Yes, No)
- Prior NP surgery (Yes, No)
- Participants with comorbid asthma only (Yes, No)
- Participants with NSAID-ERD only (Yes, No)
- Prior systemic corticosteroids use up to two years prior to first dose of study treatment (Any, None)
    - This will be identified as any medications up to two years prior to the first dose of study treatment with 'Reason for Use' marked 'CRS Polyps' on the 'Prior and Concomitant Medications' eCRF page. In addition, the medication must be coded to ATC level 2 'CORTICOSTEROIDS FOR SYSTEMIC USE' and the coded preferred term must contain any of the medications in the list below:
        - Prednisone
        - Prednisolone
        - Methylprednisolone
        - Beclomethasone
        - Betamethasone
        - Dexamethasone
        - Hydrocortisone
        - Triamcinolone
- Sex assigned at birth (male, female)
- Age group (< 65 years, ≥ 65 years)
- Baseline weight (< 90, ≥ 90 kg)
- Baseline BMI (<25, ≥25 to <30, ≥30 kg/m^2)
- The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. The categories for regions will be:
    - Region Subgroup (USA and Western Europe [USA, Germany, Spain], Eastern Europe [Czechia, Poland])
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, Other, Multiple Races)

A forest plot will be used to display the LS mean difference between the active treatment group and placebo treatment group and the corresponding 95% CI for each subgroup.

9. Demographic, Other Baseline Characteristics, and Medication

9.1. Participant Disposition and Population Inclusions

The following categories will be tabulated in the disposition table using all Screened Set as the starting population:

- *Screened*. All patients in the Screened Set
- *Screen failures*.
- *Randomized*
    - Stratification factor
        - Presence of comorbid asthma and/or NSAID-ERD. Categories: Presence, Absence.
        - Prior NP Surgery. Categories: Yes, No.
- *Analysis Sets*
    - ITT
    - SAF
    - PKAS
    - PD
    - Comorbid Asthma Set
    - Immunogenicity Analysis Set
    - PPS
- *Completed the study treatment.* Categories: Yes, No.
- Reason for treatment discontinuation. Categories:
    - Adverse Event
    - Death
    - Lack of Efficacy
    - Lost to Follow-up
    - Investigator Decision
    - Pregnancy
    - Protocol Deviation
    - Subject/Guardian Decision
    - Consent Withdrawal by Subject
    - Other
- *Completed the study.* Categories: Yes, No.
- *Reason for study discontinuation. Categories:*
    - Adverse Event
    - Death
    - Lack of Efficacy
    - Lost to Follow-up
    - Investigator Decision
    - Pregnancy
    - Protocol Deviation
    - Subject/Guardian Decision
    - Consent Withdrawal by Subject
    - Other

The disposition and population inclusion data mentioned above will be listed for all participants.

9.2. Demographic and Baseline Characteristics

Participant demographics and baseline characteristics defined below will be presented in summary tables and listings for patients in the ITT set. No formal statistical comparisons will be performed.

Demographics

- Age (years): Age as collected on the electronic case report form (eCRF)
- Age group: <65, ≥ 65 years
- Sex assigned at birth: Male, Female
- Childbearing Potential (evaluated for only female participants): Yes, No
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown, Other, Multiple Races
- Region: USA and Western Europe, Eastern Europe

Baseline Characteristics

- Height (cm)
    - Height in inches will be converted to centimeters by multiplying height by 2.54
- Weight (kg)
    - Weight in pounds will be converted to kilogram by multiplying weight by 0.4536
- BMI (kg/m^2)
    - Derived as Weight(kg)/[Height$(m)^2$]
- Time (years) since CRSwNP was first diagnosed
    - Calculated as: (date ICF signed – date CRSwNP was first diagnosed + 1)/365
        - For the date CRSwNP was first diagnosed, year is expected to be known. Year and month are expected to be known if the year CRSwNP was diagnosed was either 2023 or 2024. If month and day are missing, the missing month and day will be imputed as July 1st. If only day is unknown, the unknown day will be imputed as 15th of the month.
- NPS
- Eosinophil level (10^9/L)
- Eosinophil level: <150 cells/uL, ≥150 cells/uL
- Eosinophil level: <300 cells/uL, ≥300 cells/uL

- Presence of comorbid asthma and/or NSAID-ERD: Yes, No; where 'Yes' group is further categorized as follows:
    - Presence of comorbid asthma only
        - This will be identified as records having 'Yes' to field 'Does the Subject have active comorbid Asthma?' on the 'Asthma History' eCRF
    - Presence of NSAID-ERD only
        - This will be identified as any medical history with Medical Dictionary for Regulatory Activities (MedDRA) code 10087423 and present during the baseline visit based on the 'Medical and Surgical History' eCRF page.
    - Presence of comorbid asthma and NSAID-ERD
- Prior NP Surgery: Yes, No
- Number of prior NP surgery: 0, 1, 2, ≥3
    - NP surgery will be identified as records having 'Yes' to field 'Was this a sinus surgery?' on the 'Medical and Surgical History' eCRF. NP surgery done on the same day will be counted as one surgery.
- Number of systemic corticosteroids use up to two years prior to first dose of study treatment: 0, 1, 2, ≥3
    - This will be identified as any medications up to two years prior to the first dose of study treatment with 'Reason for Use' marked 'CRS Polyps' on the 'Prior and Concomitant Medications' eCRF page. In addition, the medication must be coded to ATC level 2 'CORTICOSTEROIDS FOR SYSTEMIC USE' and the coded preferred term must contain any of the medications in the list below:
        - Prednisone
        - Prednisolone
        - Methylprednisolone
        - Beclomethasone
        - Betamethasone
        - Dexamethasone
        - Hydrocortisone
        - Triamcinolone
- MFNS (Mometasone furoate nasal spray) Percent Compliance in the 14 days prior to Visit 2
    - Compliance will be calculated based on the number of doses taken (morning and/or evening) relative to the expected dosing regimen (twice a day or once daily).
- Any use of biologics in the past: Yes, No
    - Identified as any medication started and ended prior to Visit 1 on the Prior and Concomitant Medications eCRF and the medication's preferred term is coded as one of the medications in the list below:

  - Tezepelumab
  - Depemokimab
  - Dupilumab
  - Mepolizumab
  - Benralizumab
  - Omalizumab

- Systemic corticosteroid intolerance
  - These participants will be flagged as having systemic corticosteroid intolerance if they have a record on the Medical and Surgical History eCRF with preferred term that is coded to 'Drug intolerance'

9.3. Medical History

Medical history terms will be coded using MedDRA Version 26.1.

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the ITT for each treatment group and overall. A participant experiencing more than one medical history within a given SOC and/or PT will be counted only once within that SOC and PT, respectively. Medical history will be summarized within each treatment group in the descending order of the UPB-101 treatment group by system organ class and preferred term.

In addition, a similar summary will be created but limited to records coded to the following high level terms: 'Nasal therapeutic procedures' or 'Paranasal therapeutic procedures'. Medical history findings will be listed by participant using the ITT.

9.4. Medication

All prior and concomitant medication will be classified using the Anatomical Therapeutic Chemical (ATC) classification code level 4 and preferred terms from the World Health Organization Drug Dictionary (WHO-DD) Global B3, September 2023.

Prior and concomitant medications will be summarized separately. The number and percentage of ITT participants with prior or concomitant medications will be summarized by ATC level 4 and preferred term by treatment group and overall. All medications will be summarized within each treatment group in the descending order of the UPB-101 treatment group by ATC level 4 and preferred term within a given ATC level 4 term. For each participant, the medication will be counted only once within a level 4 ATC and only once within a given preferred term level. If ATC level 4 is missing, the next higher non-missing ATC level will be used.

A by-participant listing with coded terms will also be provided along with calculated study day.

9.4.1. Prior Medication

Any medication that started prior to and did not continue past the date of first dose of study treatment will be classified as a prior medication. Partial dates will be handled as described in Section 8.3. Medications with missing end date will be considered concomitant.

9.4.2. Concomitant Medication

Medications administered at any time on or after the first dose of study drug will be classified as concomitant medications based on the ITT. Partial start and/or end dates will be handled as described in Section 8.3. Medications continuing after the first dose of study drug or missing end date will be considered concomitant.

9.4.3. Rescue Systemic Corticosteroids for CRSwNP or for Comorbid Conditions

Rescue systemic corticosteroids for CRSwNP or for comorbid conditions will be identified as any medication initiated after first dose of study treatment and indicated as “Systemic corticosteroids for CRSwNP or Comorbid conditions” on the Prior and Concomitant Medications eCRF and the medication’s preferred term contains any of the following terms from the list below:

- Prednisone
- Prednisolone
- Methylprednisolone
- Beclomethasone
- Betamethasone
- Dexamethasone
- Hydrocortisone
- Triamcinolone

A separate summary and listing of rescue systemic corticosteroids for CRSwNP or for comorbid conditions will be provided.

9.4.4. Escalation of maintenance/background treatment

Escalation of maintenance/background treatment will be identified as any medication initiated after first dose of study treatment indicated as “New treatment for CRSwNP” on the Prior and Concomitant Medications eCRF and the medication’s preferred term is coded as one of the medications in the list below:

- Tezepelumab
- Depemokimab
- Dupilumab
- Mepolizumab
- Benralizumab
- Omalizumab

A separate summary and listing of escalation of maintenance/background treatment will be provided.

9.5. Concomitant Procedures

Concomitant procedure terms will be coded using MedDRA Version 26.1.

Concomitant procedures will be summarized by MedDRA SOC and PT for the ITT for each treatment group and overall. A participant experiencing more than one concomitant procedure within a given SOC and/or PT will be counted only once within that SOC and PT, respectively. Concomitant procedure will be summarized within each treatment group in the descending order of UPB-101 treatment group frequency by system organ class and preferred term.

Concomitant procedure will be listed by participant using the ITT.

9.5.1. Rescue Treatment Procedure

Rescue treatment will be identified using the "CRSwNP/Rescue Treatment" Indication field on the Concomitant Procedure eCRF.

A separate summary and listing of rescue treatment will be provided.

9.6. Extent of Exposure

Exposure to study treatment will be summarized using the following parameters based on the data collected in the EDC:

- *Treatment Duration (weeks)*, calculated as the minimum of (date of EOT in or prior to Week 24 [plus up to 3 days], date of last dose of IP + 12 weeks; date of last assessment) – date of first dose of IP + 1 divided by 7.
- *Total number of doses received,* calculated as number of unique study drug administration records with 'Yes' for the field 'Was Study Drug Administered?' found on the 'Study Drug Administration' eCRF page.

The above parameters will be summarized for each treatment group and overall, for participants in the ITT. A listing of exposure parameters will also be provided.

9.7. Treatment Compliance

Treatment compliance will be summarized using the following parameters based on the data collected in the EDC:

- *Overdose,* will be defined as two doses given within 6-weeks of each other or more than full dose was given at an administration.
- *Number of participants not receiving full volume*, will be determined based on the information collected on the "Study Drug Administration" eCRF page and will be summarized by visit.
- *Number of expected doses.* The number of expected doses will be 2 for participants who complete up to Week 12/Visit 6. For participants who discontinued prior to Week 12/Visit 6, the total number of expected doses will be adjusted based on their last visit date. For example, if a participant discontinues after Week 8/Visit 5, the total number of expected doses will be 1.
- *Percent Compliance*, calculated as total number of doses received divided by total number of expected doses x 100.

The above parameter will be summarized for each treatment group and overall, for participants in the Safety Analysis Set. A listing of compliance parameters will also be provided.

9.8. Protocol Deviations

Syneos Health and Upstream Bio will periodically review protocol deviations and will finalize and classify (major vs minor) the deviations prior to database lock.

Major protocol deviations are defined as deviations liable to bias the evaluation of the primary efficacy endpoint and safety endpoints. The following deviations will be considered as major (non-exhaustive list):

- Non-compliance with the inclusion or exclusion criteria
- Non-compliance with the study treatment
- Intake of prohibited medication

Summaries of major protocol deviations will be summarized for the ITT by deviation categories using frequencies and proportions. A data listing of all protocol deviations will also be provided. In addition, a separate listing of COVID-19 related protocol deviations will be provided.

A summary table of as randomized strata level versus actual strata level will be summarized for the ITT using frequencies and proportions to evaluate the number of mis-stratifications on the study.

9.9. COVID-19 Visit Impacts

The novel coronavirus (COVID-19) may have an impact on the study conduct. A listing of participants impacted will be provided that includes the visit(s) impacted and visit adjustment because of COVID-19 (e.g., missed visit, abbreviated, delayed/out of window in-person visit at site, remote visit, other).

10. Efficacy

All efficacy analyses will be performed using the ITT unless specified otherwise. Provided sample SAS codes may be modified during analysis without amendment to this SAP; modifications will be limited to option statements, variable names, and contrast statements.

Descriptive statistics by treatment group will be used to assess all endpoints at Week 28 (if applicable), unless specified otherwise.

10.1. Primary Efficacy Estimand/Endpoint and Analysis

Bilateral endoscopic NPS is a physician-reported scoring system to estimate the extent or severity of Nasal Polyps (NPs) based on assessments by nasal endoscopy. Each nostril is scored on a categorical scale of 0 to 4. A higher score means worse outcome. The degree of NPs is classified in relation to fixed anatomical landmarks: 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 polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity. The total score is the sum of the right and left scores (0-8). NPS will be assessed locally at V2 only and by central readers for all timepoints (V1, V2, V6, V8). For all analyses described in this SAP, only central reader NPS results will be utilized. NPS will typically be assessed by 2 central readers. If reader 1 and 2 scores are the same, the analysis will use the mean of reader 1 and 2 scores. If the reader 1 and 2 scores differ, reader 3 score along with the reader 1 or 2 score that is closest to reader 3 score will be averaged for analysis.

The primary efficacy endpoint is the change from baseline in NPS at Week 24. The analysis will implement an estimand framework, considering ICEs that may affect the outcomes of efficacy. See Section 7 for details of the primary estimand for the primary efficacy endpoint.

10.1.1. Primary Efficacy Analysis

The primary endpoint will be tested by the following hypothesis:

$$H_0: \mu_1 - \mu_2 = 0 \text{ versus } H_1: \mu_1 - \mu_2 \neq 0$$

where μ_1 is the mean for UPB-101 and μ_2 is the mean for Placebo. The null hypothesis is that there is no difference between treatment group means whereas the two-sided alternative hypothesis is a difference between treatment group means. The hypothesis will be tested at the significance level of $\alpha = 0.05$ (two-sided) using the LSM estimate of the treatment difference obtained from the MMRM model described below.

The primary endpoint will be analyzed using MMRM with change from baseline in NPS as the dependent variable and treatment (verekitug [UPB-101] or Placebo), baseline NPS (Week 0), visit (Weeks 12 and 24), visit-by-treatment interaction, asthma and/or NSAID-ERD status (either presence of comorbid asthma and/or NSAID-ERD or absence), prior NP surgery (Yes/No), and Region (USA and Western Europe [USA, Germany, Spain]/Eastern Europe [Czechia, Poland]) as fixed effects variables, and participant as a random effect. The covariance parameters will be estimated by restricted maximum likelihood method, specifying an unstructured covariance matrix, and the degrees of freedom will be calculated using the procedure of Kenward and Roger (FDA Guideline (2019), *"Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry"*

Kenward, M. G., and Roger, J. H. (1997)). If the model does not converge using an unstructured covariance matrix, the following covariance matrix will be employed in the specified order until

convergence is met: heterogeneous Toeplitz, heterogeneous first order autoregressive, Toeplitz, auto-regressive AR(1) structure, and compound symmetric structure. LSM for each treatment arm at the Week 24 visit, difference between verekitug (UPB-101) and Placebo LSMs at the Week 24 visit, the corresponding 95% confidence interval (CI), and the p-value will be presented.

For participants who discontinued treatment (ICE 1), treatment policy strategy will be applied and observed NPS after study treatment discontinuation will be used for the analysis. For participants who used rescue systemic corticosteroids for CRSwNP or for comorbid conditions (ICE 3), treatment policy strategy will also be applied and observed NPS after rescue systemic corticosteroids for CRSwNP or for comorbid conditions will be used for the analysis. For participants who had rescue surgical treatment for CRSwNP (ICE 2) or escalation of maintenance/background treatment by adding another drug for CRSwNP (ICE 4), composite variable strategy will be applied and NPS after the start of the ICE will be replaced by worst possible value 8. All other missing NPS not affected by ICE strategies will not be imputed and missing NPS will be assumed to be missing at random (MAR).

The following is a sample SAS code for implementing the MMRM analysis:

```
ods output lsmeans=lsmeans diffs=diffs;
proc mixed data=ADEF;
      class SUBJID TRT VISIT ANSE_ST PNPSURG REGION;
      model CHG = BASE TRT VISIT TRT*VISIT ANSE_ST PNPSURG REGION
            / ddfm = kr cl alpha = 0.05 solution;
      Repeated VISIT / type = UN sub = SUBJID;
      Lsmeans TRT*VISIT/cl diff pdiff;
run;
```

where:

- ADEF is the name of the input dataset;
- SUBJID is variable representing the participant;
- TRT is the variable for the treatment groups;
- VISIT is the variable for visit;
- ANSE_ST is the variable for asthma and/or NSAID-ERD status;
- PNPSURG is the variable for prior NP surgery stratification factor;
- REGION is the variable for region;
- CHG is the variable for change in NPS from baseline at Week 24;
- BASE is the variable for baseline NPS

In addition to model results, descriptive summary statistics for baseline NPS score and change in NPS from baseline at Week 24 and the LSM with 95%CI will be presented by treatment groups.

Additionally, the number and percentage of participants experiencing each ICE event will be summarized by treatment groups.

10.1.2. Supplementary Analysis

The primary efficacy analysis described above will be repeated using the PPS.

10.1.3. Sensitivity Analysis

To test the robustness of the primary efficacy analysis, the following sensitivity analyses will be performed using the ITT:

- An analysis with observed cases only. For participants who had rescue surgical treatment for CRSwNP (ICE 2) or escalation of maintenance/background treatment by adding another drug for CRSwNP (ICE 4), NPS will not be replaced by worst possible value of 8; observed NPS will be used for analysis.
- A worst observation carried forward (WOCF) analysis will be conducted. For participants who had rescue surgical treatment for CRSwNP (ICE 2), use of rescue systemic corticosteroids for CRSwNP or for comorbid conditions (ICE 3), or escalation of maintenance/background treatment by adding another drug for CRSwNP (ICE 4), NPS results on or after an ICE will be replaced by worst observed value on or before the time of the ICE.
- An analysis using multiple imputation for missing NPS not affected by ICE data handling strategies (described in Section 10.4).

10.2. Secondary Efficacy Endpoints and Analyses

The secondary efficacy endpoints and analyses are described below. Two-sided significance level of α = 0.05 will be applied without adjustment for multiplicity. Nominal p-values will be provided. When there are reasonable number of events available for time to an event analysis, Kaplan-Meier (KM) and hypothesis test will be performed. When there are not enough events, only proportions of events or listings will be provided by treatment group.

10.2.1. Change from Baseline at Week 24 in bi-weekly mean NCS Evaluated by the NPSD

NPSD is an 11-item nasal polyposis symptoms diary. The participant is asked to record their experience with nasal polyposis over the past 24 hours (preferably in the morning) when responding to each question (nasal blockage, nasal congestion, runny nose, postnasal drip, headache, facial pain, facial pressure, sense of smell; and symptom impacts on sleep and daily activities). Participants report the severity of each symptom and symptom impact at its worst using a 4-point verbal scale (0=none to 3=severe).

The NCS will be derived from Question 2 of the NSPD, based on participant-reported evaluation of nasal congestion severity. A higher score means worse outcome.

The NCS score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the NCS at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14-days prior to Study Day 15. The rest of the bi-weekly NCS up to week 24 will be derived similarly.

After the NCS scores are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in NCS will be analyzed in a similar manner to the MMRM analysis described in Section 10.1.1.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, NCS after the start of another treatment for CRSwNP will be replaced by worst possible value 3.

In addition to model results, descriptive summary statistics for baseline NCS and change in NCS from baseline at Week 24 will be presented by treatment groups.

Two sensitivity analyses will also be conducted. WOCF analysis where participants' NCS results on or after ICE 2, ICE 3, or ICE 4 will be replaced by the worst observed value on or before the time of the ICE. In addition, an analysis using multiple imputation for missing NCS not affected by ICE data handling

strategies will be conducted (described in Section 10.4). Missing NCS will be imputed at the bi-weekly score level.

10.2.2. Change from Baseline at Week 24 in Opacification of Sinuses Measured by LMK Score Evaluated by Quantitative CT Assessment

LMK Score (Sinus Opacification Score) is a physician-reported quality staging system for evaluation of severity of Nasal Polyps (NPs) based on assessments of the sinuses by computer tomography. The LMK staging system assigns a value of 0, 1, or 2 to each of the following 5 sinuses: maxillary, anterior ethmoid, posterior ethmoid, frontal, and sphenoid. Only adjudicated central reader LMK score will be utilized for analysis.

The score assignment is:

- 0=sinus is totally patent
- 1=sinus is partially opacified
- 2=sinus completely opacified

The Osteomeatal Complex is scored either 0 if not occluded or 2 if occluded. The maximum score for each side is thus 12, with a total score determined out of 24. A higher score means worse outcome. Participants in Germany and Czechia will not have CT scans done and will not be included in the analysis.

The endpoint, change from baseline at Week 24 in opacification of sinuses measured by LMK score, will be analyzed using analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group (2 levels; verekitug [UPB-101] or Placebo), baseline LMK Score (Week 0), asthma and/or NSAID-ERD status (Two levels; either presence of comorbid asthma and/or NSAID-ERD or absence), prior NP surgery (2 levels [Yes/No]), and region (2 levels [USA and Western Europe or Eastern Europe]). The LSM for each treatment arm, difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% CI, and the p-value will be presented.

The following is a sample SAS code for implementing the ANCOVA analysis:

```
ods output lsmeans=lsmeans diffs=diffs;
proc mixed data=ADEF;
      class TRT ANSE_ST PNPSURG REGION;
      model CHG = BASE TRT ANSE_ST PNPSURG REGION;
      Lsmeans TRT /cl diff pdiff;
run;
```

where:

- ADEF is the name of the input dataset;
- TRT is the variable for the treatment groups;
- ANSE_ST is the variable for asthma and/or NSAID-ERD status;
- PNPSURG is the variable for prior NP surgery stratification factor;
- REGION is the variable for region;
- CHG is the variable for change in LMK score from baseline at Week 24;
- BASE is the variable for baseline LMK score

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, LMK score after the start of another treatment for CRSwNP will be replaced by worst possible value 24.

In addition to model results, descriptive summary statistics for baseline LMK score and change in LMK score from baseline at Week 24 will be presented by treatment groups.

10.2.3. Change from Baseline at Week 24 in bi-weekly mean DSS Evaluated by the NPSD

Loss of smell will be derived from Question 8 of the NPSD, based on participant-reported assessment of symptom severity of DSS, recalled over the past 24 hours (usually in the morning). Higher daily DSS score indicates greater severity.

The DSS score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the DSS at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14-days prior to Study Day 15. The rest of the bi-weekly DSS up to week 24 will be derived similarly.

After the DSS scores are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in DSS will be analyzed in a similar manner to the MMRM analysis described in Section 10.2.1.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, DSS score after the start of another treatment for CRSwNP will be replaced by worst possible value 3.

A sensitivity analysis using multiple imputation for missing DSS not affected by ICE data handling strategies will be conducted as well (described in Section 10.4). Missing DSS will be imputed at the bi-weekly score level.

10.2.4. Proportion of Participants Requiring Systemic Corticosteroids or NP surgery

Descriptive summary statistics that include the number and proportion of participants requiring systemic corticosteroids or NP surgery during the study will be provided by treatment groups. The use of systemic corticosteroids will be identified as described in Section 9.4.3 and NP surgery will be identified as described in Section 9.5.1.

The difference of the proportion of participants requiring systemic corticosteroids or NP surgery between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion of participants requiring systemic corticosteroids or NP surgery along with the 95% CI will be reported.

The following is a sample SAS code for implementing the chi-square test analysis:

```
ods output RiskDiffCol1=RiskDiffCol1 ChiSq = ChiSq;
proc freq data=ADEF;
  tables trt * resp / chisq riskdiff;
run;
```

where:

- ADEF is the name of the input dataset;
- TRT is the variable for the treatment groups;
- RESP is the binary variable indicating whether the participant required systemic corticosteroid or NP surgery.

10.2.5. Time to First Nasal Polyposis Surgery and/or use of Systemic Corticosteroids for Nasal Polyposis up to Week 24

The time to first NP surgery and/or time to systemic corticosteroids for NP during the treatment period will be analyzed using the Kaplan-Meier (KM) method. For participants who had NP surgery and/or systemic corticosteroids for NP during the treatment period, this is defined as: date NP surgery or use of systemic corticosteroid for NP (whichever occurs earlier) minus the date of first study drug administration plus 1. For participants without NP surgery or use of systemic corticosteroid for NP by Week 24 or discontinued the study, they will be censored at date of Week 24 (planned date if no actual Week 24 visit occurred) or study discontinuation visit whichever occurs first; this will be calculated as: date of Week 24 visit or study discontinuation date (whichever occurs earlier) minus the date of first study drug administration plus 1. The 25th, 50th, and 75th time to event will be estimated if applicable. A stratified log-rank test, stratified by asthma and/or NSAID-ERD status, prior NP surgery status, and region comparing the treatment groups will be performed and the p-value will be reported. KM curves will also be provided by treatment groups.

10.2.6. Change from Baseline at Week 24 in bi-weekly mean NPSD TSS

Daily TSS is calculated by taking the sum of the 8 equally weighted symptom non-missing items (Questions 1-8 from the NPSD).

TSS score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the TSS at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14-days prior to Study Day 15. The rest of the bi-weekly TSS scores up to Week 24 will be derived similarly.

After the TSS scores are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in TSS will be analyzed in a similar manner to the MMRM analysis described in Section 10.2.1.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, TSS after the start of another treatment for CRSwNP will be replaced by worst possible value 24.

A sensitivity analysis using multiple imputation for missing TSS not affected by ICE data handling strategies will be conducted as well (described in Section 10.4). Missing TSS will be imputed at the bi-weekly score level.

10.3. Other Efficacy Endpoints and Analyses

10.3.1. Change from Baseline over Week 24 in NPS

The change from baseline to all post-baseline visits up to Week 24 in NPS will be analyzed using the same MMRM model described in Section 10.1.1; LSM for each treatment arm at Week 12 and Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. A corresponding figure of the LSM results at each time point will also be developed.

10.3.2. Change from Baseline over Weeks 24 and 28 in bi-weekly mean NCS evaluated by the NPSD

The bi-weekly NCS derivation from Baseline to Week 24 is described in Section 10.2.1. The NCS score at Week 26 and Week 28 will also be calculated similarly.

The change from baseline over Week 24 in NCS will be analyzed using the same MMRM model described in Section 10.2.1; LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. A corresponding figure of the LSM results at each time point will also be developed.

The change from baseline over Week 28 in NCS will be summarized descriptively by treatment groups.

10.3.3. Change from Baseline over Weeks 24 and 28 in bi-weekly mean DSS evaluated by the NPSD

The bi-weekly DSS derivation from Baseline to Week 24 is described in Section 10.2.3. The DSS score at Week 26 and Week 28 will also be calculated similarly.

The change from baseline over Week 24 in DSS will be analyzed using the same MMRM model described in Section 10.2.1; LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. A corresponding figure of the LSM results at each time point will also be developed.

The change from baseline over Week 28 in DSS will be summarized descriptively by treatment groups.

10.3.4. Change from Baseline over Weeks 24 and 28 in bi-weekly mean NPSD TSS

The bi-weekly TSS derivation from Baseline to Week 24 is described in Section 10.2.6. The TSS score at Week 26 and Week 28 will also be calculated similarly.

The change from baseline over Week 24 in TSS will be analyzed using the same MMRM model described in Section 10.2.6; LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. A corresponding figure of the LSM results at each time point will also be developed.

The change from baseline over Week 28 in TSS will be summarized descriptively by treatment groups.

10.3.5. Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in NCS

The bi-weekly NCS derivation from Baseline to Week 24 is described in Section 10.2.1.

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 1 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 1 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.6. Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in DSS

The bi-weekly DSS derivation from Baseline to Week 24 is described in Section 10.2.3.

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 1 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 1 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.7. Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in NBS

The Nasal Blockage Score (NBS) will be derived from Question 1 of the NSPD, based on participant-reported evaluation of nasal blockage severity. A higher score means worse outcome.

The NBS score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the NBS at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14 days prior to Study Day 15. The rest of the bi-weekly NBS up to week 24 will be derived similarly.

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 1 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 1 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.8. Proportion of Participants at Week 24 who Achieve >= 4 Point Decrease in bi-weekly TSS

The bi-weekly TSS derivation from Baseline to Week 24 is described in Section 10.2.6.

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 4 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 4 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.9. Proportion of Participants at Week 24 who Achieve a Maximum NPS of 1 in Each Nostril

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a NPS score of 0 or 1 in each nostril will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a NPS score of 0 or 1 in each nostril between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.10. Proportion of Participants at Week 24 who Achieve a >= 1 Point Decrease in NPS

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 1 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 1 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.11. Proportion of Participants at Week 24 who Achieve a >= 2 Point Decrease in NPS

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 2 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a 2 or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.12. Proportion of Participants at Week 24 who Achieve a >= 5 Point Decrease in LMK Score

Descriptive summary statistics that include the number and proportion of participants at Week 24 who achieve a 5 or greater point decrease will be provided by treatment groups.

Participants who had rescue surgical treatment for CRSwNP or had an escalation of maintenance/background treatment by adding another drug (e.g., an unblinded biologic therapy) for CRSwNP will be imputed as non-responders.

The difference of the proportion of participants at Week 24 who achieve a *5* or greater point decrease between treatment groups will be compared using a chi-square test. The p-value from the chi-square test, and the difference in the proportion along with the 95% CI will be reported.

10.3.13. Time to Nasal Polyposis Surgery, Systemic Corticosteroids, and/or Escalation of Maintenance/Background Treatment for Nasal Polyposis up to Week 24

The time to first NP surgery, systemic corticosteroids, and/or escalation of maintenance background treatment for NP during the treatment period will be analyzed using the KM method. For participants who had NP surgery, systemic corticosteroids, and/or escalation of maintenance/background treatment for NP during the treatment period, this is defined as: date of NP surgery, systemic corticosteroid use, or escalation maintenance/background treatment for NP (whichever occured earlier) minus the date of first study drug administration plus 1. For participants without NP surgery, systemic corticosteroid, or escalation of maintenance/background treatment for NP by Week 24 or discontinued the study, they will be censored at date of Week 24 (planned date if no actual Week 24 visit occurred) or study discontinuation visit whichever occured first; this will be calculated as: date of Week 24 visit or study discontinuation date (whichever occured earlier) minus the date of first study drug administration plus 1. The 25th, 50th, and 75th time to event will be estimated if applicable. A stratified log-rank test comparing the treatment groups will be performed and the p-value will be reported as described in Section 10.2.5. KM curves will also be provided by treatment group. KM and hypothesis test will only be conducted when there are reasonable number of events available. If there are not enough events, only proportions of events or listings will be provided by treatment group.

10.3.14. Time to Nasal Polyposis Surgery for Nasal Polyposis up to Week 24

The time to first NP surgery for NP during the treatment period will be analyzed using the KM method. For participants who had NP surgery for NP during the treatment period, this is defined as: date of first NP surgery minus the date of first study drug administration plus 1. For participants without NP surgery by Week 24 or discontinued the study, they will be censored at date of Week 24 (planned date if no actual Week 24 visit occurred) or study discontinuation visit whichever occured first; this will be calculated as: date of Week 24 visit or study discontinuation date (whichever occured earlier) minus the date of first study drug administration plus 1. The 25th, 50th, and 75th time to event will be estimated if applicable. A

stratified log-rank test comparing the treatment groups will be performed and the p-value will be reported as described in Section 10.2.5. KM curves will also be provided by treatment group. KM and hypothesis test will only be conducted when there are reasonable number of events available. If there are not enough events, only proportions of events or listings will be provided by treatment group.

10.3.15. Time to Systemic Corticosteroids for Nasal Polyposis up to Week 24

The time to first systemic corticosteroids for NP during the treatment period will be analyzed using the KM method. For participants who had systemic corticosteroids for NP during the treatment period, this is defined as: date of systemic corticosteroid for NP minus the date of first study drug administration plus 1. For participants without use of systemic corticosteroid for NP by Week 24 or discontinued the study, they will be censored at date of Week 24 (planned date if no actual Week 24 visit occurred) or study discontinuation visit whichever occured first; this will be calculated as: date of Week 24 visit or study discontinuation date (whichever occured earlier) minus the date of first study drug administration plus 1. The 25th, 50th, and 75th time to event will be estimated if applicable. A stratified log-rank test comparing the treatment groups will be performed and the p-value will be reported as described in Section 10.2.5. KM curves will also be provided by treatment group. KM and hypothesis test will only be conducted when there are reasonable number of events available. If there are not enough events, only proportions of events or listings will be provided by treatment group.

10.3.16. Incidence of ADAs during the Study (including the Post-treatment Follow-Up Period)

The proportion of participants with positive verekitug (UPB-101) antidrug antibodies will be summarized at all timepoints: Baseline, Week 12, Week 24, and Week 28 visits. In cases of positive results for ADA evaluation, the ADA titer will be evaluated. The titer of ADA positive results will be descriptively summarized at Baseline, Week 12, Week 24, and Week 28 visits.

In addition, a summary of treatment-emergent ADA incidence, treatment-boosted ADA incidence, and overall ADA incidence will be provided. Participants will be classified to have treatment-emergent ADA if they had a baseline ADA sample that was negative and had any positive ADA samples post-baseline. Participant will be classified to have treatment-boosted ADA if they had a baseline ADA sample that was positive and had any post-baseline ADA titer >4 fold increase relative to the baseline ADA titer. Overall ADA incidence will be derived as the sum of participants with treatment-emergent or treatment-boosted ADA.

A listing of verekitug (UPB-101) antidrug antibodies results will also be provided. Samples from participants receiving placebo may be excluded from analysis.

10.3.17. In Participants with ADAs, Incidence of Nab during the Study (including the Follow-Up Period)

In participants with ADAs (the immunogenicity analysis set [IAS]), the proportion of participants with verekitug (UPB-101) neutralizing antibodies will be summarized at Baseline, Week 12, Week 24, and Week 28 visits using descriptive statistics.

A listing of verekitug (UPB-101) Nab results will also be provided.

10.3.18. Change from Baseline over Week 24 in ACQ-6 in Participants with Comorbid Asthma

Effect of adequacy of asthma control in participants with comorbid asthma (the Comorbid Asthma Set [CAS]) will be assessed by the participant completion of the ACQ-6. The ACQ-6 has 6 questions; Participants will be asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 6-point scale (0=no impairment; 6=maximum impairment). ACQ-6 is completed during clinic visits at Day 1 (Visit 2), Week 12, Week 24, and Week 28.

The questions are equally weighted and the ACQ score is the mean of the questions and, consequently, ranges from 0 (totally controlled) to 6 (severely uncontrolled).

ACQ-6 records not done in a participant's native language will be excluded from analysis. These records will be identified as any records containing the following verbatim text in the protocol deviation description field from the protocol deviation dataset:

- 'ACQ-6 not done in native language of the subject.'
- 'ACQ-6 not done in the native language of the subject.'

If the ACQ-6 impacted record is a baseline value, then all subsequent change from baseline values will be excluded from analysis even if the subsequent assessments are done in the participant's native language.

Descriptive summary statistics for baseline ACQ-6 and change in ACQ-6 from baseline at Week 12, Week 24, and Week 28 will be presented by treatment groups for participants in the Comorbid Asthma Set.

In addition, the change from baseline over Week 24 in ACQ-6 will be analyzed using an MMRM model in a similar manner to the analysis described in Section 10.2.1; LSM for each treatment arm at each post baseline time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. If the model has issues converging, only descriptive summary statistics will be provided.

10.3.19. Change from Baseline over Week 24 in FEV_1 in Participants with Comorbid Asthma

Spirometry assessment will be done in participants with comorbid asthma (the Comorbid Asthma Set [CAS]). FEV_1 will be measured by spirometry using the equipment provided by a central vendor.

Descriptive summary statistics for baseline FEV_1 and change in FEV_1 from baseline at Week 12 and Week 24 will be presented by treatment groups for participants in the Comorbid Asthma Set.

In addition, the change from baseline over Week 24 in FEV_1 will be analyzed using an MMRM model in a similar manner to the analysis described in Section 10.2.1. LSM for each treatment arm at each post baseline time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented. If the model has issues on converging, only descriptive summary statistics will be provided.

A listing of spirometry assessment data will be provided for the following parameters:

- Forced Expiratory Volume in 1 Second (L)
- FEV1/FVC (%)
- Forced Expiratory Flow 25-75% (L/s)

- Forced Inspiratory Vital Capacity (L)
- Forced Vital Capacity (L)
- Peak Expiratory Flow (L)
- Percent Predicted FEV1 (%)
- Percent Predicted FEV1/FVC (%)
- Percent Predicted Forced Vital Capacity (%)
- V backextrapolation ex (L)

10.3.20. Change from baseline to Week 24 in three Dimensional CT volumetric measurement of the paranasal sinuses

The change from baseline to Week 24 in three-dimensional CT volumetric measure will be analyzed using percent occupied by disease. Percent occupied by disease will be calculated as: volume of mucosa divided by the sum of volume of mucosa and volume of air, times 100. A higher value means worse outcome.

Percent occupied by disease will be analyzed by the following anatomic sinus cavity: total all sinuses, total ethmoid sinuses, and total maxillary sinuses.

The change from baseline at Week 24 in percent occupied by disease by each anatomic sinus cavity will be analyzed in a similar manner to the ANCOVA analysis described in Section 10.2.2.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, percent occupied by disease after the start of another treatment for CRSwNP will be replaced by worst possible value 100.

In addition to model results, descriptive summary statistics for baseline percent occupied by disease and change in percent occupied by disease from baseline at Week 24 will be presented by treatment groups.

10.3.21. Change from Baseline over Weeks 24 and 28 in bi-weekly mean Sleep Score Evaluated by the NPSD

Bi-weekly mean Sleep score will be derived from Question 9 of the NPSD, based on participant-reported assessment of symptom severity of sleep, recalled over the past 24 hours (usually in the morning). Higher daily Sleep score indicates greater severity.

The Sleep score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the Sleep score at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14-days prior to Study Day 15. The rest of the bi-weekly Sleep score up to week 28 will be derived similarly.

After the Sleep scores are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in Sleep score will be analyzed in a similar manner to the MMRM analysis described in Section 10.2.1. LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, Sleep score after the start of another treatment for CRSwNP will be replaced by worst possible value 3.

The change from baseline over Week 28 will be summarized descriptively by treatment groups.

10.3.22. Change from Baseline over Weeks 24 and 28 in bi-weekly mean Daily Activities Score Evaluated by the NPSD

Bi-weekly mean Daily Activities score will be derived from Question 10 of the NPSD, based on participant-reported assessment of symptom severity of daily activities, recalled over the past 24 hours (usually in the morning). Higher Daily Activities score indicates greater severity.

The Daily Activities score will be calculated as the 14-day average of daily non-missing scores, and will be derived bi-weekly, starting from Baseline and up to Week 24. The bi-weekly score will be set to be missing if 8 or more daily scores are missing. For example, the Daily Activities score at baseline will be calculated as the 14-day average of daily non-missing scores prior to Study Day 1 (i.e., 14-day average score from Study Day -14 to Study Day -1, inclusive). The Week 2 score will be calculated similarly, using daily non-missing scores from 14-days prior to Study Day 15. The rest of the bi-weekly Daily Activities score up to week 28 will be derived similarly.

After the Daily Activities scores are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in Daily Activities score will be analyzed in a similar manner to the MMRM analysis described in Section 10.2.1. LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, Daily Activities score after the start of another treatment for CRSwNP will be replaced by worst possible value 3.

The change from baseline over Week 28 will be summarized descriptively by treatment groups.

10.3.23. Change from Baseline over Weeks 24 and 28 in bi-weekly mean NBS Evaluated by the NPSD

The bi-weekly NBS derivation from Baseline to Week 24 is described in Section 10.3.7. The NBS at Week 26 and Week 28 will also be calculated similarly.

After the NBS are derived bi-weekly from baseline to Week 24, the change from baseline at Week 24 in NBS will be analyzed in a similar manner to the MMRM analysis described in Section 10.2.1. LSM for each treatment arm at each bi-weekly time point until Week 24, the mean difference between verekitug (UPB-101) and Placebo LSMs, the corresponding 95% confidence interval (CI), and the p-value will be presented.

A similar strategy as the primary efficacy analysis will be applied for the ICE. However, for ICE 2 and ICE 4, NBS after the start of another treatment for CRSwNP will be replaced by worst possible value 3.

The change from baseline over Week 28 in NBS will be summarized descriptively by treatment groups.

10.4. Multiple Imputation Approach for Primary Efficacy and Select Secondary Endpoints

There are two types of missing data patterns: monotone and non-monotone missing pattern. A monotone missing pattern occurs when the missing values follow a sequential structure across time points. If a dataset is arranged such that if a value is missing in one time point and all subsequent values are also missing, the pattern is monotone. Non-monotone missing pattern occurs when missing values are scattered without any sequential structure. There is no clear relationship between missing values across time points.

Where missing data occur and are not affected by ICE data handling strategies, a multiple imputation (MI) approach will be employed, based on a pattern-mixture method accounting for baseline characteristics in predicting the specified outcome. The MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. The number of imputations will be 10 per MI step, representing the set of 10 plausible values obtained from a prediction model based primarily on observed data. The number of imputations and/or burn-in iterations may be increased if there are convergence issues. Small number of imputations have been shown to be adequate based on relative efficiency (Rubin, D. B. (1996)) For example, with 30% missing information, five imputations are needed for 94% efficiency. Therefore, 10 imputations at each step should be sufficient for this study.

Where non-monotone missing data exist for the primary and secondary endpoints (NCS, DSS, and TSS), such missing data will be considered missing at random (MAR). Monotone missing data may exist as well and will be considered missing not at random (MNAR).

The full MI approach will comprise of 4 steps as follows:

1. Non-monotone MAR Imputation Step (10 imputations): Where non-monotone missing data exist, a Markov Chain Monte Carlo (MCMC) approach will be used for multiple imputation, using all available participant NPS data by treatment group at Baseline, Week 12, and Week 24, as per Section 10.4.1. Imputed values that fall outside the plausible range for a given endpoint will be capped at the nearest boundary of that range. For example, imputed values for the NPS endpoint will be constrained between 0 and 8.
2. Monotone missing not at random (MNAR) Imputation Step (10 imputations): Where monotone missing data exist, the missing data will be imputed using a regression modelling approach, with predictors based on all available participant data from the placebo group, as per Section 10.4.2.0
3. Analysis Step: The analysis as described in Section 10.4.3 is conducted for each of the 10x10=100 imputations.
4. Combining Step: Rubin's rule (SAS PROC MIANALYZE) is used as described in Section 10.4.4 to combine the 100 point estimates and standard errors, in order to provide a single point estimate, confidence interval and p-value (Rubin, D. B. (1976), Rubin, D. B. (1987))

10.4.1. Non-Monotone MAR Imputation Step

Any participant with non-monotone missing data will be multiple imputed using a non-monotone MCMC approach and specifying a joint distribution of NPS data at Baseline, Week 12, and Week 24 by treatment group. Ten imputations will be specified. This approach treats non-monotone missing data as MAR.

Example SAS syntax is as follows:

```
proc mi data=DATIN out=DATOUT1 (rename=(_IMPUTATION_=MCIMP)) nimpute=10 seed=XXXXX;
        BY TRT;
        var BASE W12NPS W24NPS;
        MCMC chain=multiple impute=monotone;
        em  maxiter=3500 converge = 0.00001;
```

```
run;
```

If the observed missingness pattern is already monotone, this step will be skipped and proceed to the next step. In this scenario, instead of 10 imputations, 100 imputations will be conducted for the monotone MNAR imputation step.

10.4.2. Monotone MNAR Imputation Step

Once the initial MAR non-monotone imputation step has been conducted, the monotone MNAR imputation step will be conducted for the primary estimand. Any participant with monotone missing data for the NPS will subsequently be multiple imputed using a MNAR regression modelling approach, including factors for treatment group, asthma and/or NSAID-ERD status, prior NP surgery, region, and baseline value for NPS, utilizing all data from the placebo arm to inform the imputation of missing data across both treatment arms. This approach treats the missing data as being MNAR and applies a "return-to-control" handling approach. The monotone MNAR imputation step will be conducted for 10 imputations, so after this step there will be 10 x 10 = 100 imputations available for the primary estimand. Factors may be removed if there's not enough data. Imputed values that fall outside the plausible range for a given endpoint will be capped at the nearest boundary of that range.

Example SAS syntax is as follows:

```
proc mi data = DATOUT1 out = DATOUT2 nimpute=10 seed=XXXX
    minmaxiter=3500;
   by MCIMP;
   class TRT ANSE_ST PNPSURG REGION;
   monotone reg(/details);
   mnar model (W12NPS / modelobs = (TRT="Placebo"));
   mnar model (W24NPS / modelobs = (TRT="Placebo"));
   var ANSE_ST PNPSURG REGION BASE W12NPS W24NPS;
run;
```

For secondary efficacy endpoints (NCS, DSS, and TSS), missing data will be multiple imputed at the bi-weekly score level and will follow similar methodology used for the primary estimand multiple imputation approach.

10.4.3. Analysis Step

For the primary estimand, each of the 10 x 10 = 100 imputations will be analyzed using MMRM described in Section 10.1.1.

Example code for MMRM:

```
ods output lsmeans= lsmeans diffs= diffs;
proc mixed data = DATOUT2;
   by _IMPUTATION_ MCIMP;
   class SUBJID TRT VISIT ANSE_ST PNPSURG REGION;
   model CHG = BASE TRT VISIT TRT*VISIT ANSE_ST PNPSURG REGION
         / ddfm=kr cl alpha = 0.05 solution;
   Repeated VISIT / type = UN sub = SUBJID;
   lsmeans TRT*VISIT / cl diff pdiff;
```

```
run;
```

The secondary endpoints will be analyzed in a similar manner.

10.4.4. Combining Step

SAS Proc MIANALYZE will be used to combine the 100 point estimates for the difference in LSMeans and standard errors, allowing appropriate statistical inference as described below:

```
PROC MIANALYZE DATA=DATIN ALPHA=0.05;
  MODELEFFECTS Estimate;
  STDERR StdErr;
  ODS OUTPUT ParameterEstimates=DATOUT;
RUN;
```

10.4.5. Seeds to be Used for Imputation

Variable	Step	Seed
NPS	Non-Monotone MAR	7963458
	Monotone MNAR	2186435
NCS	Non-Monotone MAR	8462091
	Monotone MNAR	7458305
DSS	Non-Monotone MAR	1406791
	Monotone MNAR	8315345
TSS	Non-Monotone MAR	4589863
	Monotone MNAR	8623431

11. Pharmacokinetics

The pharmacokinetic endpoint of this study is a summary of verekitug (UPB-101) exposure as measured by the serum concentrations. The PKAS will be used for the PK analysis.

11.1. PK Sampling Schedule

Blood samples for serum concentration analysis of verekitug (UPB-101) will be collected at the following time points from subjects administered verekitug (UPB-101) and placebo: Visit 2 pre-dose, Visit 3, Visit 4, Visit 6 pre-dose, Visit 7, Visit 8, Visit 9, EOT (if different than visit 8), and EOS (if different than visit 9).

11.2. Serum PK Endpoint

The serum concentrations of verekitug (UPB-101) will be summarized by nominal time points at baseline, during treatment, and follow-up periods. Population PK and/or PK/PD analyses may be conducted and presented in a separate report.

11.3. Presentation of Concentration Data

11.3.1. Handling of Missing Data

No imputation of missing PK concentrations is done.

11.3.2. Handling of the Difference between the Scheduled and the Actual Sampling Times

For all sampling times, the actual sampling times relative to dosing will be calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in days and rounded off to three decimal digits, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs. If the actual sampling times is absent, then nominal time will be used for tabulation and graphical representation purposes.

11.3.3. Presentation of Individual PK Data

All serum concentration below the limit of quantification (BLQ) will be treated as zero for summaries and graphical representations and listed as originally displayed in the bioanalytical dataset. The sampling time relative to dosing for pre-dose samples will be treated as zero. If the actual sampling time is missing, then planned time will be used if deemed appropriate. Samples taken far outside the sampling windows may be excluded from by-time point summary statistics. The PK data will be presented in ug/mL.

11.3.4. Listing and Presentation of PK Concentrations

The following presentations of subject serum concentration data will be provided for verekitug (UPB-101) for the PKAS:

- Listing, including subject, time point (actual and nominal), treatment and serum concentrations by Visit.
- Table, summary of serum concentration by nominal sampling time at each time point (n, number and percentage BLQ, arithmetic mean, SD, SEM, arithmetic coefficient of variation (CV(%)) (calculated as 100*SD/mean), median, minimum, and maximum) by Visit.

The following figures will be produced on the linear and semi-log scale:

- Figure, line plot of individual serum concentrations versus actual elapsed sampling time from first dose with all subjects in the same figure.

- Figure, mean ± SD serum concentration versus nominal sampling time at each Visit.

For serum concentrations, the final results will be reported as they appear in corresponding dataset.

12. Pharmacodynamics

The PD Analysis Set will include all participants in the safety analysis set who received study treatment and have at least one evaluable PD sample.

12.1. PD Sampling Schedule

Blood samples and nasal secretions will be collected at the following time points from subjects administered verekitug (UPB-101) and placebo: Visit 2 pre-dose, Visit 4, Visit 6 pre-dose, Visit 7, Visit 8, EOT (if different than visit 8).

12.2. PD Endpoint

The absolute and percent change from baseline over Week 24 in blood and nasal secretion PD biomarkers will be summarized. Population PK/PD analyses may be conducted and presented in a separate report.

12.3. [redacted]

[redacted]

12.4. Handling of Values Outside the Range of the Assay

For values that are below the lower limit of quantification (LLOQ), i.e., 'below level of quantification (BLQ)' or 'not detected', they will be imputed to ½ LLOQ value for the calculation of means and standard deviation. This will allow us to calculate an imputed change from baseline if the post-baseline value falls below LLOQ. However, if the baseline value is imputed, that subject will not be included for the 'change from baseline' and 'percent change from baseline' calculations. In the unlikely event of an above limit of quantification (ALQ) value, they will be excluded from analyses. All these BLQ, not detected, and ALQ data will still be presented in their original form in the listings.

13. Safety

The population used for safety analyses will be the SAF. Safety will be assessed based on adverse event (AE), clinical laboratory data, ECG parameters, physical examinations, and vital signs. Safety data analyses will be performed by actual treatment group i.e., 'as treated'.

13.1. Adverse Events

The definitions of AEs and SAEs are described in Appendix 3 of the study protocol. TEAEs are defined as an adverse event that first occurred on or after the date of the first dose of study drug or was present before the date of the first dose of study drug but worsens following the initiation of the study drug.

AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 26.1.

An overall summary of TEAEs will be provided by treatment group and overall, including the number of events and the number and percentage of participants who experience at least one of the following:

- AEs (includes AEs that occurred prior to first dose of study drug)
- TEAEs
- Treatment-related TEAEs
- Treatment-emergent SAEs
- Treatment-related, treatment-emergent SAEs
- Fatal TEAEs
- Grade 3 or higher TEAEs
- TEAEs leading to study drug discontinuation
- Treatment-emergent Adverse Events of Special Interest (AESI)

The incidence and frequency of TEAEs will also be summarized by SOC and PT for each treatment group and overall. The summary will be presented by descending frequency by SOC and PT in the Verekitug (UPB-101) column and then alphabetically within PT for TEAEs with the same frequency.

The following summary of TEAEs by SOC and PT will be presented:

- TEAEs by SOC and PT
- TEAEs by PT
- Treatment-related TEAEs, by SOC and PT
- Treatment-emergent SAEs, by SOC and PT
- Treatment-related, treatment-emergent SAEs, by SOC and PT
- Grade 3 or higher TEAEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs by SOC, PT, and maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade

At each level of incidence summarization, a participant is counted only once at the SOC level and only once at each PT within the SOC level. For summaries by SOC, PT, and maximum CTCAE grade, a participant is counted only once at the highest CTCAE grade for which the event occurred at the SOC level and the highest CTCAE grade level for each unique PT within that SOC level.

An AE will be considered treatment-related if the relationship attribution designation is missing. If CTCAE grade is missing for an AE, the event will be summarized under “missing”. Partial dates will be imputed per Section 8.3 to determine whether an AE is TEAE.

All AEs will be listed by treatment, participant, and chronologically by date of AE onset. AE dates will be listed as recorded in the eCRF (without imputation for partial dates). Additional AE listings of SAEs, TEAEs leading to study drug discontinuation will also be provided.

13.1.1. Treatment-emergent Adverse Events of Special Interest

The treatment-emergent AESIs will be indicated on the eCRF.

An overall summary of treatment-emergent AESIs will be provided by treatment group and overall, including the number of events and the number and percentage of participants who experience at least one of the following:

- Treatment-emergent anaphylaxis reaction
- Treatment-emergent immune complex disease and type
- Treatment-emergent severe infections
- Treatment-emergent helminth parasitic infection requiring treatment
- Treatment-emergent injection site reaction (ISR) that is CTCAE Grade 3 or higher

Within each of the categories above, AESIs will further be summarized by SOC and PT.

13.2. Clinical Safety Laboratory Tests

Clinical laboratory tests include hematology, serum chemistry, urinalysis, and coagulation, identified in Table 10-3 of the study protocol and performed according to the Schedule of Activities in study protocol, Table 1-1.

Numeric results from the hematology, chemistry, urinalysis, and coagulation panels will be summarized by visit using descriptive statistics, including the observed and change from baseline values. For hematology and chemistry panels, box plot of the change from baseline by visit will also be generated.

Shift from baseline of reference range indicator results (i.e., low, normal, or high as assessed using the reference normal range) at each post-baseline visit will be summarized using counts and percentages of participants for applicable parameters in the hematology, chemistry, and coagulation panels.

For hematology, additional summaries of counts and percentages of participants meeting the following criteria will be summarized by visit and at any timepoint post-baseline:

- Hemoglobin: < 110 g/L (for female subjects)
- Hemoglobin: < 125 g/L (for male subjects)
- Hemoglobin: Change from baseline > 15 g/L
- White Blood Count: > 15 (x 10^9/L)
- White Blood Count: < 2.5 (x 10^9/L)
- Lymphocytes: < 0.75 (x 10^9/L)
- Neutrophils: < 1.5 (x 10^9/L)
- Eosinophils: > 1.5 (x 10^9/L)
- Platelets: < 125 (x 10^9/L)
- Prothrombin Time: > 1.11 x upper limit normal (ULN)
- Partial Thromboplastin Time: > 1.2 x ULN

For chemistry, additional summaries of counts and percentages of participants meeting the following criteria will be summarized by visit and at any timepoint post-baseline:

- Sodium (Hyponatremia): < 132 mmol/L
- Sodium (Hypernatremia): > 145 mmol/L
- Potassium (Hypokalemia): < 3.5 mmol/L
- Potassium (Hyperkalemia): > 5.2 mmol/L
- Glucose (Hypoglycemia): < 3.61 mmol/L
- Glucose (Hyperglycemia): > 6.94 mmol/L
- Urea Nitrogen > 9.28 mmol/L
- Creatinine > 150 mcmol/L
- Calcium (Hypocalcemia) < 2.0 mmol/L
- Calcium (Hypercalcemia) > 2.74 mmol/L
- Phosphorous (Hypophosphatemia) < 0.74 mmol/L
- Creatine Phosphokinase > 1.5 x ULN
- Albumin (Hypoalbuminemia): < 28 g/L
- Total Protein (Hypoproteinemia): < 55 g/L
- Alkaline phosphate: > 2.0 x ULN
- Alanine transaminase: > 2.5 x ULN
- Aspartate transaminase: > 2.5 x ULN
- Bilirubin: > 1.5 x ULN
- Cholesterol: > 5.44 mmol/L

In addition, to evaluate the potential for serious drug-induced hepatotoxicity, a scatter plot of maximum total bilirubin versus maximum alanine transaminase and aspartate transaminase will be generated. By participant safety laboratory listings will be generated.

If laboratory values are provided as '<X' (i.e., below the limit of detection) or '>X', these numeric values are set to X. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Pregnancy test results will be listed but not summarized.

13.3. Vital Signs

Vital signs (temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) will be measured according to the Schedule of Activities in study protocol, Table 1-1.

Descriptive summaries of actual values and changes from baseline will be presented for each visit (on dosing days, only pre-dose will be summarized) by treatment group. Box plot of change from baseline by visit will also be generated. An additional summary of vital signs on dosing days will be created including actual values at pre-dose, post-dose, and within 30 minutes prior to discharge along with change from pre-dose at each dosing day.

Vital sign data will be listed chronologically by participant and visit for each vital sign parameter.

13.4. Electrocardiograms

A standard 12-lead ECG (Heart Rate, RR, PR, QRS, QT, QTc will be performed locally at the site and obtained according to the Schedule of Activities in study protocol, Table 1-1.

QTcF will also be derived as follows:

$$QTcF = \frac{QT}{RR^{1/3}}$$

Descriptive summaries of observed numeric ECG parameter values and changes from baseline will be presented for each visit and timepoints (for applicable visits) by treatment group.

In addition, shift from baseline of investigator's ECG interpretation (i.e., Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) at each post-baseline visit and timepoint (for applicable visits) will be summarized using counts and percentages of participants.

For QTcF, additional summaries of counts and percentages of participants meeting the following criteria will be summarized by visit and at any timepoint post-baseline:

- Absolute QTcF interval prolongation:
    - QTcF interval > 450 msec to ≤ 480msec
    - QTcF interval > 480 msec to ≤ 500msec
    - QTcF interval > 500 msec
- Change from baseline in QTcF interval:
    - QTcF interval increase from baseline > 30 msec to ≤ 60msec
    - QTcF interval increase from baseline > 60 msec

By participant listing of ECG data will be provided.

13.5. Physical Examination

Physical examination will be performed at timepoints described in the Schedule of Activities in study protocol, Table 1-1.

Physical examination results will be listed but not summarized.

14. Interim Analyses

A blinded interim analysis will be conducted prior to completion of study enrollment. The objective of the blinded interim analysis is to decide on the final sample size prior to completion of study enrollment.

The analysis will be based on blinded data (i.e., only overall results will be provided; participants treatment assignments will not be revealed). The details of the blinded interim analysis described in Appendix 20.2. Sample size may be increased but will not exceed 1.5 times the original size. Sample size reduction will not be considered. Any decision to increase the sample size will be made early enough to inform sites before enrollment closes. The Sponsor will determine the final sample size, ensuring adequate statistical power for the primary outcome.

15. Changes from Analysis Planned in Protocol

Due to a shorter than anticipated enrollment period, only one DBL will be conducted for this trial. Accordingly, the planned analyses of primary and secondary objectives using the data from the first database lock (protocol section 9) will not be performed as the plan of multiple database locks has been canceled.

For the primary efficacy endpoint analysis, missing NPS (not affected by ICE with treatment policy and composite variable strategies) will not be imputed by multiple imputation approach as the MMRM method already assumes any missing data are missing at random. In addition, region was added as a covariate for the MMRM modelling. Lastly, statistical hypothesis testing will be conducted using a two-sided test at the significance level of 0.05. The original planned analysis with multiple imputation will be conducted as a sensitivity analysis.

While the protocol initially specified the use of the Cochran-Mantel-Haenszel (CMH) test for stratified categorical analysis, we have opted to use the chi-square test instead. This decision was based on the anticipated distribution of the data. It is anticipated that there's a high likelihood of sparse data across strata, resulting in numerous empty or low-frequency cells. Such sparsity would undermine the validity and interpretability of the CMH test. Based on the anticipated distribution of the data, chi-square test is therefore considered more appropriate for the planned analysis.

The endpoint, *Change from Baseline over Week 24 in the proportion of participants requiring systemic corticosteroids or NP surgery,* was revised as *Proportion of participants requiring systemic corticosteroids or NP surgery through Week 24.*

The following endpoints not specified in the study protocol have been added:

- Proportion of Participants at Week 24 who Achieve a >= 1 Point Decrease in NPS
- Proportion of Participants at Week 24 who Achieve a >= 2 Point Decrease in NPS
- Proportion of Participants at Week 24 who Achieve a >= 5 Point Decrease in LMK score
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in NCS
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in DSS
- Proportion of Participants at Week 24 who Achieve >= 1 Point Decrease in NBS
- Proportion of Participants at Week 24 who Achieve >= 4 Point Decrease in TSS
- Time to nasal polyposis surgery, systemic corticosteroids, and/or escalation of maintenance/background treatment for nasal polyposis up to Week 24
- Time to nasal polyposis surgery for nasal polyposis up to Week 24
- Time to systemic corticosteroids for nasal polyposis up to Week 24
- Change from Baseline over Weeks 24 and 28 in Sleep Score evaluated by the NPSD

- Change from Baseline over Weeks 24 and 28 in Daily Activities evaluated by the NPSD
- Change from Baseline over Weeks 24 and 28 in NBS evaluated by the NPSD

16. Reference List

FDA Guideline (2019), “Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry”

Kenward, M. G., and Roger, J. H. (1997). “Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood.” Biometrics 53:983–997

Rubin, D. B. (1976), “Inference and Missing Data,” Biometrika, 63, 581–592

Rubin, D. B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons

Rubin, D. B. (1996). “Multiple Imputation after 18+ Years.” Journal of the American Statistical Association 91:473–489

17. Programming Considerations

All TFLs, and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications.

17.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered in Word format (Rich Text Format) or portable document format pdf
- Numbering of TFLs will follow ICH E3 guidance

17.2. Table, Figure, and Listing Format

17.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

17.2.2. Headers

- All output will have the following header at the top of each page:

  Upstream Bio, Inc
  Protocol UPB-CP-03

- Draft/Final Run DDMMMYYYY

- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page.

17.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z First Line of Title
Second Line of Title if Needed
ITT Analysis Set

17.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include ‘unit’ in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of participants in the analysis set.
- The order of treatments in the tables and listings will be the active treatment group then the Placebo group, followed by a total column (if applicable).

17.2.5. Body of the Data Display

17.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

17.2.5.2. *Table Conventions*

- Units will be included where available.
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more participants.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8) if n(%) is specified in the table or for the item). Unless otherwise noted, for all percentages, the number of participants in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'
- The percentage of participants will normally be calculated as a proportion of the number of participants assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of

selecting the denominator, usually the appropriate number of participants exposed. Details will be described in footnotes as necessary.

- For categorical summaries (number and percentage of participants) where a participant can be included in more than one category, a footnote will be added describing whether the participant is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

17.2.5.3. *Listing Conventions*

- Missing data will be represented on participant listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on participant listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the participant will be output as 'N/A', unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

17.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

17.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible

- Participant specific footnotes are avoided, where possible

- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

18. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. Syneos Health SOPs Developing Statistical Programming and Validation Plan (3920), End-to-End Process of the Production of Study Data Tabulation Model (SDTM) (3921), and End-to-End Process of the Production of Analysis Datasets (ADaM) and Tables, Figures, and Listings (3922) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency, and commenting and by review of the produced output.

Syneos Health SOP Peer Review and Quality Review of Pharmacokinetic Activities (2767) describe the quality control procedures that are performed for PK analysis and outputs.

19. Index of Tables, Figures, and Listings

Table, figure, and listing (TFL) shells are provided in a separate document.

20. Appendices

20.1. Schedule of Activities

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Participant Demography	X								
Medical/Surgical History	X	X							
Medication History	X	X							
CRSwNP History	X	X							
Asthma History[d]	X	X							
Height	X								
Weight	X							X	X
Complete Physical Examination	X					X		X	
Targeted Physical Examination		X	X	X	X		X		X
Record concomitant medication		<==========>							
Dispense and/or Download Diary	X								
Assess Background INCS Usage	X								
Assess MFNS (or equivalent) Usage		X	X	X	X	X	X	X	X
Treatment:									
Randomization/ Study Intervention Assignment		X							
Administration of Study Intervention		X				X			
Injection Site Reactions Assessment		<==========>							

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Efficacy:									
Nasal Endoscopy for NPS[e]	X	X				X		X	
Sinus CT Scan (CT scans not performed in Germany)[f]	X							X	
Daily Diary/PRO (NPSD)	<==========Background MFNS or equivalent, Nasal Polyposis Symptoms==========>								
Training and/or Compliance with Daily Diary/PRO (NPSD)	X	X	X	X	X	X	X	X	X
Spirometry (in participants with comorbid asthma only)	X[g]					X		X	
ACQ-6 (in participants with comorbid asthma only)		X				X		X	X
Safety:									
AE/SAE Review	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X[h]	X	X	X	X[h]	X	X	X
12-lead ECG (local reading)[i]	X	X[i]				X		X	X
Laboratory Testing:									
Hematology[j]	X	X	X	X	X	X	X	X	X
Chemistry	X	X		X		X	X	X	X
Coagulation	X								X
Viral Serology	X								
Urinalysis	X	X		X		X		X	X

Procedure [a, b]	**Screening Period**	**Treatment Period**							**Follow-up Period**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT**[c]	**9/EOS**
Study Week	**-5 to -3**	**Day 1 (WK 0)**	**WK 2**	**WK 4**	**WK 8**	**WK 12**	**WK 18**	**WK 24**	**WK 28**
Visit Window (±days)		**NA**	**± 2**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Serum Pregnancy Test (for POCBP only)/FSH as applicable[k]	X							X	X
Urine Pregnancy Test (POCBP only)[k]		X	X	X	X	X	X		
Serum PK		X	X	X		X	X	X	X
Serum ADA and NAb		X				X		X	X
Serum for IgA, IgE[l], IgG, and IgM		X		X		X	X	X	
Serum for PD biomarkers [redacted]		X		X		X	X	X	
Nasal Secretion Sampling for Biomarkers [redacted]		X		X		X	X	X	

ACQ-6=Asthma Control Questionnaire-6, ADA=antidrug antibody, AE=adverse event, CRSwNP=chronic rhinosinusitis with nasal polyps, CT=computed tomography, ECG=electrocardiogram, EOS=end of study, EOT=end of treatment, FSH=follicle-stimulating hormone, IgA=immunoglobulin A, [redacted], INCS=intranasal corticosteroid, [redacted], MFNS=mometasone furoate nasal spray, NAb=neutralizing antibody, NPS=nasal polyp score, NPSD=nasal polyposis symptom diary, PD=pharmacodynamic, PK=pharmacokinetics, POCBP=participants of childbearing potential, PRO=patient reported outcome, SAE=serious adverse event, [redacted]

a. Expected order of activities is detailed in Protocol Section 8. It is noted that the CT or nasal endoscopy procedure may occur on a different date than the study visit date due to restrictions in scheduling these procedures for the participant.
b. In an unfavorable situation, wherein study centers are closed, or in case of restrictions or for any other local/regional factors, or for any reason wherein participant's travel to the study center is not feasible due to conveyance issue, home visit(s), phone call visit(s), and/or remote assessments and/or site monitoring may be considered. To maintain/preserve data integrity (versus risking losing the data points), the assessments will be labeled as having been obtained remotely (home or non-site location) and will be subject to a separate statistical analysis (Protocol Section 8).
c. Participants who discontinue treatment early will, if at all possible, remain in the study to be evaluated for clinical observation and safety monitoring.
d. For participants with comorbid asthma.

e. Nasal endoscopy will be performed after all other efficacy assessments have been completed for the respective visit. At Visit 2, the Investigator will review the Visit 1 results from the central reader to confirm entry criteria have been met, as well as reconfirm eligibility based on Visit 2 endoscopy local reading. On dosing visits, endoscopy will be performed pre-dose.
f. Computed tomography scan will be performed during the Screening Period (at Visit 1 or after, provided results are available prior to Visit 2). In case of early termination, the Investigator will determine whether to perform an EOT CT scan, based on the age, clinical condition, and overall risk to the participant and timing of the EOT visit. (CT scans not performed in Germany.)
g. To accommodate withholding of background therapies prior to spirometry, screening spirometry may be performed on a separate day during the Screening Period.
h. On dosing visits, vital signs will be measured at pre-dose, post-dose, and within 30 minutes prior to discharge.
i. At Visit 2 there will be 2 ECGs performed: pre-dose and within 30 minutes prior to discharge.
j. Hematology panel includes blinded/masked eosinophils, monocytes and basophils starting at Visit 2 (unblinded/unmasked prior to Visit 2).
k. Serum and urine pregnancy test (for POCBP): A negative result of serum pregnancy test at Visit 1 and urine pregnancy test must be obtained prior to randomization at Visit 2. Participants <50 years old who are amenorrheic for >12 months who are considered menopausal must have a FSH ≥ 40 IU/mL at Visit 1. At the EOS Visit, a home pregnancy testing kit will be issued to participants who are POCBP to be used at approximately Day 120 post-last dose. Results should be reported to the Investigator.
l. IgE will be blinded/masked for all applicable visits.

20.2. [redacted]

[redacted]