CLINICAL STUDY PROTOCOL

A Phase 2, Double-Blind, Placebo-Controlled, Parallel-Group, Multiple Dose Study to Investigate Etokimab (ANB020) in Adult Subjects with Chronic Rhinosinusitis with Nasal Polyposis

Short Title:	Efficacy, Safety, and Pharmacokinetic Profile of Etokimab in Adults with Chronic Rhinosinusitis with Nasal Polyposis
Protocol Number:	ANB020-006
National Clinical Trial (NCT) Identified Number:	NCT03614923
Lead Investigator:	[redacted]
IND Sponsor:	AnaptysBio, Inc. 10421 Pacific Center Court, Suite 200 San Diego, CA 92121 United States
Amendment:	3
Protocol Date:	06 February 2020
Safety Reporting:	[redacted]

Sponsor Signature Page

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, International Council on Harmonisation Good Clinical Practice [ICH GCP] guidelines) and the protocol.

_____ _____

[redacted]
Date

Chief Medical Officer
AnaptysBio, Inc.

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Substantive changes to Amendment 3 are summarized below.

The overall rationale for this amendment is to correct inconsistencies in objectives and endpoints listed throughout the document and correct administrative errors.

Summary of Changes for ANB020-006 Protocol Amendment 3

Affected Section(s)	Summary of Revisions Made	Rationale
Global	• Minor editorial and grammatical updates	• Correction.
Synopsis (secondary and exploratory objectives), Section 3	• Moved Quality of Life (QoL) objective from secondary objectives to exploratory objectives	• QoL endpoints will not be used for decision-making for future studies with etokimab.
Synopsis (secondary and exploratory objectives), Section 3	• Re-ordered secondary effectiveness endpoints to reflect the hierarchical order of statistical testing. • Identified secondary efficacy endpoints, which will undergo hierarchical statistical testing. All other efficacy endpoints were considered as exploratory endpoints. • Revised the list of endpoints in each section so that each relevant section of the protocol displays the same endpoints.	• Hierarchical testing of secondary efficacy endpoints is being implemented as part of the Statistical Analysis Plan, therefore the protocol should also reflect the order of hierarchical testing of these endpoints. • All other secondary efficacy endpoints will not be used for decision making for future studies with etokimab. • The protocol was previously inconsistent in the presentation of endpoints in the different sections of the protocol.

Affected Section(s)	Summary of Revisions Made	Rationale
Synopsis (Study Population),Section 5.1 (inclusion #2)	• Removed phrase “for both nostrils” from bilateral NPS score.	• “Bilateral” and “both nostrils” are redundant.
Synopsis (Participant Duration)	• Updated the duration description to include the breakdown of the duration of each period in the study.	• Clarification.
Section 1.3 (Schedule of Activities, footnotes k and l),	• Removed the sentence “Samples should be obtained prior to administering study drug if an administration coincides with the visit.”	• Removed for redundancy.
Section 1.3 (Schedule of Activities, footnote j), Section 6.2.5	• Added language that subjects with ongoing TEAEs or treatment-emergent SAEs at the time of discharge after the first injection of study drug should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant.	• Clarification for subject safety.
Section 1.3 (Schedule of Activities, footnote w)	• Added text to clarify that endoscopies performed onsite should be completed after all other study assessments and prior to dosing on that day.	• Consistency.
Section 2.2.2.1	• Added text that GLP-compliant toxicology and toxicokinetic studies also included a 26-week study.	• Updated information.
Section 3	• Updated table to match the changes to the objectives and endpoints made in the Synopsis. Includes reduction of the number of secondary efficacy endpoints; moved remaining efficacy endpoints to exploratory, moved QoL objective to exploratory; wording revisions.	• The protocol was previously inconsistent in the presentation of objectives and endpoints in the different sections of the protocol.
Section 5.1 (Inclusion #3e)	• Reworded the criterion	• Clarification.
Section 6.3.1	• Updated the first sentence to match the study description	• Consistency.
Section 7.1	• Clarified that subjects who discontinue early from study treatment, but not from the study as a whole, will be encouraged to complete their remaining clinic visits according to the SoA.	• For internal consistency with the analysis described in Sections 9.4.2.1.1 and 9.4.2.3.
Section 8.1.5	• Corrected the timing of CT scans	• Corrected for consistency.
Section 8.1.6	• Added text to clarify that the baseline biopsy should be obtained before administration of the study drug.	• Clarification.
Section 8.1.7	• Added text that genomic analysis will us a validated assay and only samples within the window of sample stability will be analyzed.	• Clarification.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 8.1.8.2	• Corrected number of levels in each dimension from 3 to 5.	• Correction
Section 8.2.4	• Updated section to match the SOA	• Consistency.
Section 8.2.6	• Added text to clarify that subjects only need to remain onsite for 2 hours following the first dose of study drug.	• Clarification.
Section 8.3	• Deleted text that specified “approximately 5 mL” of whole blood samples will be collected.	• Detailed information about blood samples will be provided in the laboratory manual.
Section 8.5	• Specified that only samples from etokimab-dosed subjects will be evaluated for anti-drug antibody (ADA).	• Clarification.
Section 9.1	• Section was revised to only discuss co-primary endpoints.	• Details of secondary endpoint analyses will be provided in the Statistical Analysis Plan (SAP).
Section 9.2	• Corrected the percentage of dropouts expected from 15% to 18% in the sample size estimate.	• Correction
Section 9.3	• Heading title was changed to “analysis sets.” • The ITT analysis set was removed. • Description of the full analysis set (FAS) and Per Protocol (PP) were corrected.	• The term “analysis set” is being used throughout the protocol. • The ITT set is not being used for any planned analyses; the FAS set is being used for efficacy analyses.
Section 9.4.2 and Table 3	• Revised text of Section and Table 3 to reflect analysis of co-primary endpoints. • Updated Table 3 to reflect planned changes to the analysis of secondary endpoints and exploratory efficacy endpoints and the restructuring of the secondary/exploratory efficacy endpoints	• In accordance with ICH E9, we are limiting the number of secondary endpoints and moving the additional endpoints being evaluated to exploratory.
Section 9.4.2.1	• Section heading was removed and text has become part of Section 9.4.2.	• Changed for consistency.
Section 9.4.2.1.1, Section 9.4.2.1.2	• Updated text of the co-primary endpoints. • Changed the term “dropout” to “treatment discontinuation.”	• Changed for consistency. • The term “treatment discontinuation” is more accurate in these sections as subjects could stop treatment but remain in the study.
Section 9.4.4.1	• Added the term “study discontinuations” to the description of the tabular presentation of subject disposition.	• Clarification.
Section 9.4.2.2	• Heading changed to Analysis of the Secondary and Exploratory Endpoint(s).	• Heading change reflects updated section content.

Affected Section(s)	Summary of Revisions Made	Rationale
	• Modified text to indicate that details of secondary and exploratory analyses will be provided in the SAP. • Moved PK analysis text to this section and added a note that additional PK parameters may be evaluated if needed.	• Most of the analysis details will be presented in the SAP and are not needed in the protocol. • PK endpoints are secondary, so the text was compressed into a single section.
Section 9.4.2.3	• Deleted section.	• This text was not needed due to the changes made in Section 9.4.2.2.
Section 9.4.3.1	• Clarified that TEAEs and SAEs will be presented as summaries; AEs (all) and SAEs will be presented as by-subject listings.	• The previous text was unclear about what AE data would be presented as summaries vs listings.
Section 9.4.3.2	• Deaths will now be presented only as a by-subject listing	• The number of deaths is expected to be small, therefore a summary of deaths was not considered additive for assessing safety.
Section 9.4.5	• Interim analysis will now include both co-primary endpoints. • Updated interim analysis to be performed when approximately 84 randomized subjects have completed Week 8 • Text regarding the conditional power was deleted.	• Details of the statistical analyses will be described in the SAP and in the DSMB analysis plan, as appropriate.
Section 9.4.9	• Deleted section.	• Text from this section was moved to Section 9.4.2.2.

Substantive changes to Amendment 2 are summarized below.

The overall rationale for this amendment to correct inclusion and exclusion criteria based in input from participating Investigators, to update interim analysis details, and correct administrative errors.

Summary of Changes for ANB020-006 Protocol Amendment 2

Affected Section(s)	Summary of Revisions Made	Rationale
Title Page	• Lead investigator updated	• Dr. Simon is not participating in the study
Synopsis (1.1) Section 5.1 Inclusion Criteria number 2	• Updated minimum bilateral Nasal Polyp Score from 5 to 4 • Updated minimum score required from 2 to 1 in each nostril	• Input provided by participating clinical Investigators with strong patient management experience

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.3 Schedule of Activities	• Corrected footnote errors	• Correction of errors and ensure alignment with Inclusion/Exclusion criteria
Section 5.1 Inclusion Criteria	• Increased upper limit of body mass index from 38 to 42 kg/m^2	• Subject safety and aligning criteria for enrolled subjects • Input provided by participating clinical Investigators with strong patient management experience
Section 5.2 Exclusion Criteria	• Updated method for confirming aspirin-exacerbated respiratory disease diagnosis (exclusion 4) • Reduced interventional treatment time restriction from 6 months to 3 months (exclusion 7) • Clarified clinical significance for abnormal electrocardiogram findings (exclusion 10) • Clarified antibiotic treatment exclusion applies to systemic antibiotics (exclusion 12) • Updated smoking pack-years and clarified smoking restrictions (exclusion 15) • Clarified blood screening for hepatitis B (exclusion 16) • Updated QuantiFERON® test requirements (exclusion 17) • Clarified initiation of immunotherapy requirements (exclusion 24)	• Focusing on subject safety and aligning criteria in subjects being enrolled • Input provided by participating clinical Investigators with strong patient management experience • Clarifications • Corrections
Section 5.4 Screen Failures	• Added instruction for rescreening	• Provide clarification
Section 6.1.2 Dosing and Administration	• Added instruction for injection site area	• Provide clarification
Section 6.2.2 Etokimab formulation, appearance, packaging, and labeling	• Updated appearance information	• Correction of error
Section 8.1.3	• Clarified timings for nasal peak inspiratory flow recordings	• Clarification
Section 8.1.5	• Updated permitted computed tomography (CT) scans of the sinuses to allow scans collected within 3 months of screening to be used	• Focusing on patient safety during rescreening process and for recently assessed subjects

Affected Section(s)	Summary of Revisions Made	Rationale
Section 9.2 Sample size determination	• Added details of sample size calculation • Updated statistical power calculations to reduce percentage of dropouts from 20% to 15% and the number of subjects per treatment arm from 35 to approximately 33	• To clarify the hypothesis testing strategy for the co-primary endpoints • Review of available information indicates lower rate acceptable
Section 9.4.2.1 Analysis of co-primary endpoints 9.4.2.1.1 First co-primary endpoint 9.4.2.1.2 Second co-primary endpoint	• Added confirmation of when statistical significance will be declared • Added details for hierarchical testing • Updated confidence interval and significance level	• To clarify the hypothesis testing strategy for the co-primary endpoints
Section 9.4.5 Planned interim analysis	• Updated interim analysis to be performed when approximately 100 randomized subjects have completed Week 8 • Updated interim analysis to use conditional power instead of O'Brien-Fleming type boundaries	• To avoid issues in boundary calculation based on Week 8 completion
Appendix A	• Clarified instructions prohibited medications	• Provide clarification

Substantive changes to Amendment 1 are summarized below.

The overall rationale for Amendment 1 reflects the key comments provided by clinical experts, safety staff, and provides clarity regarding procedures.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study have been incorporated into this amendment for clarification and administrative purposes only and are not summarized below.

Summary of Changes for ANB020-006 Protocol Amendment 1

Affected Section(s)	Summary of Revisions Made	Rationale
Entire protocol	• Updated grammatical errors and clarified existing information	• Accuracy and completeness
Title Page	• Added Safety Reporting Details	• Accuracy and completeness
Study Design, Schedule Of Events	• Clarified screening window: Maximum 31 days of screening	• Clarification
Study Design: Synopsis (1.1) Schedule of Activities (1.3) Overall Design (4.1)	• Clarified mometasone furoate nasal spray (MFNS) use and run-in timeline • Added language on patient compliance of approximately 80% throughout the study including during Screening • Clarified that MFNS is provided by Sponsor • Clarified instruction on lowering dose if necessary	• Accuracy and clarification
Synopsis (1.1)	• Corrected Secondary Endpoints to capture appropriate assessments and align with Section 3 (Objectives and Endpoints)	• Correction
Synopsis (1.1)	• Updated study participants from 102 to 105	• Correction
Figure 1	• Updated patient arm descriptions and added MFNS to the diagram for clarity	• Clarification
Section 1.3 Schedule of Activities (SoA)	• Removed Week 2/Day 15	• Correction, removed unnecessary visit
Section 1.3 Schedule of Activities (SoA)	• Added additional procedures to SoA in accordance with existing protocol procedures	• Provide clarification
Section 1.3 Schedule of Activities (SoA)	• Added additional detail on study windows and in footnotes	• Provide clarification and accuracy

Affected Section(s)	Summary of Revisions Made	Rationale
Objectives: Section 3	• Corrected Secondary Endpoints to capture appropriate assessments and align with Section 1.1 (Synopsis) • Added secondary endpoint • Corrected QoL sub-bullets • Added Exploratory Endpoint	• Correction and improve accuracy • Assure assessments are analyzed correctly
Section 5.1 Inclusion Criteria	• Increased maximum age from 65 to 70 years old at time of consent • Clarified bilateral scoring process • Clarified symptoms (bulleted symptoms) • Increased body mass index (BMI) from 36 to 38 kg/m^2 • Added upper limit of normal (ULN) lab value criteria • Added compliance criteria for MFNS usage during Screening • Added compliance criteria for Nasal peak inspiratory flow (NPIF) completion during Screening	• Focusing on patient safety and aligning criteria in patients being enrolled • Input provided by participating clinical Investigators with strong patient management experience
Section 5.2 Exclusion Criteria	• Increased SNOT-22 minimum score from ≤ 7 to ≤ 15 at Screening • Added Aspirin-exacerbated respiratory disease (AERD) diagnosis to exclusion criteria • Clarified nonsteroidal treatment exclusion details • Added additional detail to ischemic cardiovascular disease to clarify cerebrovascular events and time (within 1 year of Screening) • Added vaping to nonsmoking guidelines • Corrected reference to FEV_1 percent predicted guidelines • Corrected high dose medication error • Clarified definition of nasal surgery • Removed maximum number of prior nasal polyp surgeries • Reduced time since last surgery from 6 months to 3 months	• Focusing on patient safety and aligning criteria in patients being enrolled • Input provided by participating clinical Investigators with strong patient management experience • Corrections
Section 5.4 Screen Failures	• Removed 30 day restriction for rescreening	• Input provided by participating clinical Investigators
Section 6.1.2 Dosing and Administration	• Added instruction for subcutaneous injection procedures	• Provide clarification
6.2.4 Investigational Product Preparation	• Updated header to specify “Investigational Product”	• Correction

Affected Section(s)	Summary of Revisions Made	Rationale
	• Removed "unblinded" team/preparer language	
Section 6.2.6 Mometasone Furoate Nasal Spray Formulation, Appearance, Packaging, and Labeling	• Added information on MFNS	• Provide clarification
Section 6.2.6 Mometasone furoate Nasal Spray Formulation-dosing Instructions	• Added information on dosing and instruction for decreasing, and compliance.	• Provide clarification • Provide additional information on required MFNS usage
6.3.1 Randomization	• Removed unblinded staff language and explained kit assignment	• Correction
6.5.1 Rescue Medicine	• Updated discontinuation language should subjects require rescue medication	• Correction • Provide clarification
7.1 Discontinuation of Study Intervention	• Updated/added details to better define discontinuation of study intervention	• Correction • Provide clarification
7.2 Participant Discontinuation/Withdrawal from the Study	• Updated section to require subject withdrawal for: ○ Pregnancy ○ Abnormal liver function tests as defined in the protocol • Removed language allowing optional continuation in the study treatment discontinuation	• Assuring patient safety
8.1.1 Nasal Endoscopy and Nasal Polyp Score (NPS)	• Added details to clarify timing of procedure and study windows	• Provide clarification
8.1.3 Nasal Peak Inspiratory Flow	• Added details to clarify collection procedures, timing, and compliance	• Provide clarification
8.1.5 Disease-Specific Tests and Assessments	• Added details requirements and timing of procedure, and study windows	• Provide clarification
8.1.8.4 Excluded Medications Prior to Lung Function Assessments	• Reduced asthma medication withholding timelines prior to spirometry from: ○ Twice daily and once daily inhalers (LABA/LAMA) reduced from 24 hrs. to 12 hrs ○ LTRA reduced from 24 hrs. to 12 hrs ○ Theophyllines reduced from 24hrs to 12 hrs ○ Rescue SABA reduced from 6 hours to 4 hours	• Focusing on patient safety • Input provided by participating clinical Investigators with strong patient management experience
8.2.1 Clinical Laboratory Data	• Removed incorrect information regarding antibody sample analysis	• Correction

Affected Section(s)	Summary of Revisions Made	Rationale
8.3 Pharmacokinetics, 8.5 Immunogenicity	• Updated sample collection information • Updated PK and ADA processing	• Clarification
8.6.5 Adverse Event Reporting	• Clarified requirements AE collection and recording	• Provide clarification
8.6.6 Serious Adverse Event Reporting 8.6.9 Reporting of Pregnancy	• Updated contact information	• Correction
Section 9 –Statistical Considerations	• Corrected secondary endpoint analysis details • Updated number of subjects per arm • Full Analysis Set -Corrected typographical error • Secondary Efficacy Analysis: provided clarification • Exploratory Efficacy: provided clarification and detail	• Corrections requested upon additional review of statistician • Correction/updates based on primary and secondary endpoints
10.1.5 Key Roles and Study Governance	• Updated Medical Monitor contact details	• Correction
Appendix B	• Pregnancy testing: corrected confirmation requirements	• Correction and clarification
Appendix D	• Updated Polyp Size descriptions for scoring	• Provide clarification in definitions • Input provided by participating clinical Investigators with strong patient
Appendix E	• Updated Sino-Nasal Outcome Test (SNOT-22) Questionnaire	• Correction received from license holder

Investigator's Agreement

PROTOCOL TITLE: A Phase 2, Double-Blind, Placebo-Controlled, Parallel Group, Multiple Dose Study to Investigate Etokimab (ANB020) in Adult Subjects with Chronic Rhinosinusitis with Nasal Polyposis

PROTOCOL NO: ANB020-006

VERSION: Amendment 3

This protocol is a confidential communication of the sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCPs) and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor or designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, ICH GCP and applicable United States (US) Code of Federal Regulations (21 CFR). The principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent forms (ICFs), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the ICFs must be obtained before any participant is enrolled. Any amendments to the protocol, ICFs, recruitment materials, and all participant materials will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved prior to implementation; a determination will be made regarding whether a new informed consent needs to be obtained from participants who provided informed consent, using a previously approved ICF.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 2, Double-Blind, Placebo-Controlled, Parallel Group, Multiple Dose Study to Investigate etokimab (ANB020) in Adult Subjects with Chronic Rhinosinusitis with Nasal Polyposis

Study Description: This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multiple dose study designed to assess the efficacy of different doses and dose regimens of etokimab compared to placebo in adults with moderate to severe chronic rhinosinusitis with nasal polyposis (CRSwNP). This study will also assess the safety, tolerability, and pharmacokinetics (PK) of etokimab. The effects of etokimab on subjects with moderate to severe CRSwNP will be monitored over 24 weeks.

All subjects will enter a run-in period of between 20 and 31 days on mometasone furoate nasal spray (MFNS) of 2 actuations (50 µg/actuation) in each alternate nostril twice daily (BID), total daily dose of 400 µg, at Visit 1, unless the subject is intolerant to BID intranasal corticosteroids (INCS) in which case, subjects can stay on the lower dose regimen (at the clinical judgment of the investigator). MFNS will be provided by the Sponsor. Compliance must be verified by the site prior to randomization.

Objectives:

Primary Objective:

- To evaluate the efficacy of etokimab compared to placebo in the treatment of subjects with CRSwNP following a 16-week treatment period (change from baseline using co-primary endpoints)

Secondary Objectives:

- To evaluate the effectiveness of etokimab compared to placebo in subjects with CRSwNP in relieving clinical symptoms.
- To assess the safety and tolerability of etokimab in subjects with CRSwNP compared to placebo following a 16-week treatment period
- To assess the PK of etokimab in human serum in subjects with CRSwNP following subcutaneous (SC) administration

Endpoints:

Co-Primary Endpoints:

- Change from baseline to Week 16 in bilateral endoscopic Nasal Polyp Score (NPS)
- Change from baseline to Week 16 in Sino-Nasal Outcome Test (SNOT-22) scores

	Secondary Efficacy Endpoints: • Time to first response (≥1 point improvement) in NPS • Responder analysis: response defined as a reduction of at least 1 point from baseline to Week 16 in NPS • Responder analysis: response defined as a reduction of at least 12 points from baseline to Week 16 in SNOT-22 • Change from baseline to Week 16 in sense of smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT) Other Secondary Endpoints • Incidence of adverse events (AEs) and treatment-emergent AEs (TEAEs) • Incidence of serious adverse events (SAEs) • Changes in clinical laboratory tests (hematology, chemistry, and urinalysis) • Changes in vital signs (blood pressure [BP], temperature, respiration rate, and pulse rate) • Changes in electrocardiogram (ECG) parameters • Immunogenicity (anti-drug antibody [ADA} and neutralizing ADA) • Apparent clearance (CL/F) • Apparent volume of distribution • Maximum concentration (Cmax) • Time of maximum concentration (t_{max}) • Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{tau}) • Apparent terminal half-life ($t_{1/2}$) will also be determined for etokimab after SC administrations, as possible
Study Population:	Approximately 100 adults between the ages of 18 and 70 years of age with CRSwNP with a minimum bilateral Nasal Polyp Score of 4 out of 8 (maximum score) (with minimum score of 1 in each nostril) despite completion of a prior INCS treatment for at least 8 weeks before Screening. Presence of at least 2 of the following symptoms prior to Screening: nasal blockade/obstruction, nasal congestion, or nasal discharge (anterior/posterior nasal drip), facial pain/pressure, and/or reduction in or loss of smell.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Approximately 25 investigative sites across the United States (US) are expected to participate in this study. Approximately 100 subjects will be enrolled (approximately 33 evaluable subjects per treatment arm).
Description of Study Intervention:	Etokimab or matching placebo for SC injection: • Sterile etokimab in single-use glass vials; each vial will contain 100 mg/mL of etokimab. • Sterile placebo in identically matched single-use glass vials; each vial will contain no active drug product. See Figure 1 for dosing regimen.

Study Duration: Study duration will last approximately 12 months.

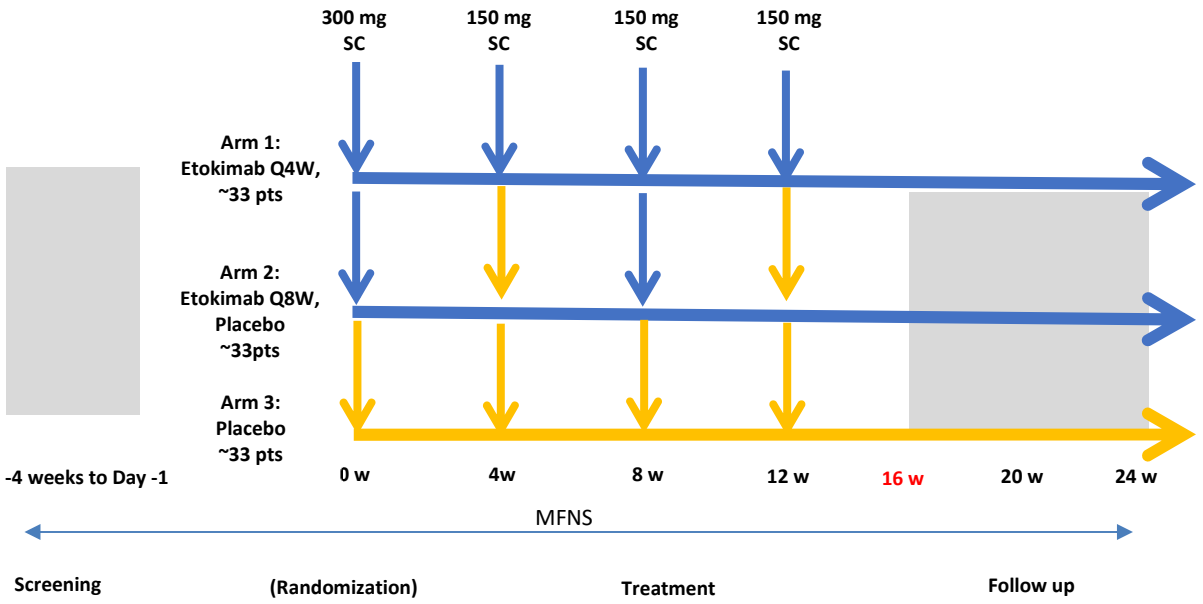
Participant Duration: Participant duration includes:

- 4-week screening period (maximum of 31 days) with a minimum MFNS run-in period of 20 days
- 16-week treatment period
- 8-week follow-up

The total participant duration is expected to be up to 28 weeks.

1.2 SCHEMA

Figure 1. Study Schema for Protocol ANB020-006



Legend:	
Etokimab = blue line	Primary endpoints assessed = red type
Placebo = yellow line	Gray shading = nontreatment period

NOTE: MFNS will be provided to all subjects as standard of care for all 3 groups.

Abbreviations: MFNS=Mometasone Furoate nasal spray
SC=subcutaneous(ly)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Phase	**Screening**	**Treatment**						**Safety Follow-Up**	
Week	**-4 to 0**	**0**	**1[a]**	**4**	**8**	**12**	**16/EOT**	**20**	**24/EOS/ETV**
Study Day	**-31 to -20***	**1d**	**5± 1d**	**29±3d**	**57±3d**	**85±3d**	**113±5d**	**141±5d**	**169±5d**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed Consent	X								
IXRS: Subject Screening/Randomization/Drug Dispensing/Treatment Completion	X	X		X	X	X	X		
Inclusion/Exclusion Criteria[b]	X	X							
Medical History (Including Prior CRSwNP Therapy)	X								
Height	X								
Physical Examination[c]	X	X					X		X
Vital Signs Including Weight[d]	X	X		X	X	X	X	X	X
12-Lead ECG[e]	X	X					X		X
Follicle Stimulating Hormone[f]	X								
Pregnancy Test[g]	X	X		X	X	X	X	X	X
Drugs of Abuse (urine), HIV, Hepatitis B and C Viral Testing, TB Test (QuantiFERON® Gold)[h]	X								
Hematology, Chemistry[i]	X	X	X	X	X	X	X		X
Urinalysis	X	X					X		X
Study Drug Injection[j]		X		X	X	X			
Pharmacokinetics[k]		X	X	X	X	X	X	X	X
Immunogenicity[l]		X		X	X	X	X	X	X
FEV_1 (Spirometry) [m]		X[y]		X	X	X	X		
ePRO Device Dispensation/Collection[n]		X							X

Phase	**Screening**	**Treatment**						**Safety Follow-Up**	
Week	**-4 to 0**	**0**	**1[a]**	**4**	**8**	**12**	**16/EOT**	**20**	**24/EOS/ETV**
Study Day	**-31 to -20***	**1d**	**5± 1d**	**29±3d**	**57±3d**	**85±3d**	**113±5d**	**141±5d**	**169±5d**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
NPIF readings collected via Diary[o]	←	—	—	—	—	—	—	—	→
Adverse Event Monitoring		←	—	—	—	—	—	→	
Concomitant Therapy[p]	←	—	—	—	—	—	—	—	→
Nasal Endoscopy (centralized Nasal Polyp Score)[b, w]	X	X		X	X	X	X		X
CT Scan (Lund & 3D- correct accordingly)[x]		X					X		
Smell Test (UPSIT)[q]		X			X		X		
SNOT-22	X	X		X	X	X	X		X
Visual Analogue Scale (VAS)		X (Weekly via ePro Device)							
QoL (SF-36, EQ-5D)		X		X	X	X	X		X
Nasal Polyps Related Resource Questionnaire		X		X	X	X	X		X
ACQ-7[r]		X		X	X	X	X		X
Nasal Polyp Biopsies[s, t]		X					X		
Stored DNA Sampling[t, u]		X							
Whole Blood RNA Sampling[t,u]		X		X			X		X
MFNS – distribute and verify usage[v]	←	—	—	—	—	—	—	—	→

Abbreviations: ACQ-7 = 7-item Asthma Control Questionnaire; CRSwNP = Chronic Rhinosinusitis with Nasal Polyposis; d = day(s); CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; ePRO = electronic patient-reported outcome; EQ-5D = EuroQol-5D for measuring QoL; ETV = Early Termination Visit; HIV = human immunodeficiency virus; IXRS = Interactive Web Response System; NPIF = nasal peak inspiratory flow; QoL = quality of life; SF-36 = Short Form-36 Health Assessment; SNOT-22 = Sino-Nasal Outcome Test; TB = tuberculosis; UPSIT = smell identification test; VAS = visual analogue scale.

Footnotes on the next 2 pages.

* During the screening window patients must use MFNS for a minimum of 20 days prior to Day 1 (maximum screening window is 31 days). Screening procedures can be conducted up to Day -1 if necessary.

[a] Visit must occur 5 days (±1 day) after Visit 2.

[b] Inclusion/exclusion criteria are based on all screening assessments, Visit 1 nasal endoscopy, and laboratory results. Week 0/Day 1 pre-dose assessments are to be reviewed before enrollment.

[c] A complete physical examination will be performed at the screening visit. All other physical examinations should be abbreviated and address associated complaints or findings and any other assessments required to evaluate adverse events.

[d] Vital signs assessments should be performed before blood sampling and before injection of study drug at each study visit where administered. Blood pressure readings should be obtained after approximately 15 minutes of rest in a seated position.

[e] 12-Lead ECG should be performed after 10 minutes of rest in a supine position and before the blood sample is collected. ECG must be conducted on ECG machine provided by ERT for the ANB020-006 clinical trial.

[f] Follicle stimulating hormone may be used to confirm menopausal status in female subjects as needed.

[g] Pregnancy testing is only required for women of childbearing potential (WOCBP). A serum test will be performed at the screening visit; urine pregnancy tests will be performed at treatment and follow-up visits. Testing must be performed before injection of study drug at Weeks 0, 4, 8, and 12. A negative result must be obtained at Visits 1 and 2 before subject may be randomized.

[h] HIV 1 and 2, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and *Mycobacterium tuberculosis* (TB) will be assessed. Subjects with an indeterminate QuantiFERON® TB Gold result at Screening will be allowed 1 retest.

[i] Hematology and chemistry: Blood samples will be taken before injection of study drug, after the ECG and vital signs assessments.

[j] Subject is required to remain onsite for 2 hours post-dose for observation at Week 0 (Day 1). Subjects with any ongoing treatment-emergent AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant. Subjects are not required to remain onsite after follow-up injections (Weeks 4, 8, and 12) unless deemed necessary by the Investigator, if there have been injection site reactions, or other AEs are noted.

[k] Pharmacokinetics blood samples will be collected for all subjects at the following time points:

- Visit 2/Week 0: prior to dosing on Day 1.
- Visit 3/Week 1: Visit 3 can occur 3 to 5 days after Visit 2.
- Week 4, 8, 12: prior to dosing.
- Week 16, 20, and 24: any time at each visit.

[l] Immunogenicity blood samples will be collected for all subjects at the following time points:

- Visits 2 (Week 0), 4 (Week 4), 5 (Week 8), and 6 (Week 12): prior to dosing.
- Visits 7 (Week 16), 8 (Week 20), and 9 (Week 24): any time at each visit.

[m] All subjects should have the result of FEV_1 (% of predicted normal as defined by the Global Initiative for Asthma) recorded in the source on Day 1 and at all the other scheduled visits during the treatment period. Every effort should be made to perform FEV_1 assessment at the same time at each visit. If a subject with active asthma's $FEV_1 \leq 60\%$ on Day 1, then the subject will not be randomized. FEV_1 assessment should be conducted on the spirometry machine provided by ERT for the ANB020-006 clinical trial.

[n] The ePRO device will be provided to subjects on Day 1 upon confirmation of randomization. Subjects should be trained on log in and completion of NPIF distribution within the ePro device. The subjects should bring the ePRO device to each visit. The ePRO device should be returned to the site at the Week 24 (EOS) visit. Detailed instructions will be provided separately in the Procedures Manual.

[o] Peak Nasal Inspiratory Flow Meters will be provided to patients during the screening visit and patients will be instructed on use and recording requirements. NPIF values will be recorded on a paper diary during Screening (for 1 week/7 consecutive days). Diary must be returned to the study coordinator at the Day 1 dosing visit. Following randomization, eDiaries will be distributed and NPIF values will be recorded directly in the device.

[p] Concomitant therapy will include pharmacologic and nonpharmacologic therapies.

[q] Testing must be performed before injection of study drug at Weeks 0 and 8.

[r] The ACQ-7 will be assessed only in subjects with an active asthma disease.

[s] Optional polyp biopsies will be collected from subjects who indicate approval on ICF, in study centers with the capability to conduct the procedure.

[t] Samples will be collected before injection of study drug on Day 1.

[u] Optional sampling for exploratory analysis of DNA and RNA, requiring separate pharmacogenetic consent acknowledgment in ICF.

[v] MFNS bottles will be distributed and used bottles collected at monthly visits to assess use. Subjects should be approximately 80% compliant with usage during Screening and throughout the study. During Screening subjects must complete a minimum of a 20 day run-in using MFNS prior to Day 1.

[w] Endoscopy can utilize study windows to ensure procedure can be completed prior to dosing. Day 1 Endoscopy can occur up to 5 days prior to Day 1 clinic visit. If endoscopy is performed on site it should be completed after all other study assessments are done and prior to dosing on dose days.

[x] Day 1 CT must be collected prior to dosing on Day 1. If necessary, the Day 1 CT can be collected during Screening, prior to Day 1, however all efforts should be made to conduct CT after subject screening labs have been reviewed and it is determined subject is likely eligible for the study. Note: CTs collected within 3 months prior to randomization (Day 1) can be utilized in lieu of a new Day 1 CT if the necessary imaging requirements are present.

[y] Day 1 spirometry should be assessed prior to randomization to ensure inclusion/exclusion criteria are met

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic rhinosinusitis (CRS) is a heterogeneous disease which manifests with mucosal inflammation of the nasal cavity and paranasal sinuses. Chronic rhinosinusitis can be divided into 3 distinct clinical syndromes: CRS with nasal polyposis (CRSwNP) accounting for 20 to 33 percent of all CRS cases, and CRS without nasal polyposis and allergic fungal rhinosinusitis accounting for 60 to 65% and 8 to 12% of all CRS cases, respectively (*Meltzer et al., 2004*). CRSwNP is characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex. It is the most aggressive form of CRS and causes significant morbidity and leads to a diminished quality of life in CRS patients.

Current treatment options for CRSwNP are limited and typically include nonsystemic treatment with nasal corticosteroids, systemic corticosteroids, antibiotic therapy, and the surgical removal of polyps. Many patients achieve disease control with these standard nonsystemic treatments. However, due to disease severity, treatment-related adverse reactions, or other factors, some patients do not achieve adequate disease control. Relapses after surgery are common in patients with CRSwNP, and thus, there is need for long term therapeutic control in CRS patients.

CRSwNP is often associated with other atopic diseases, with up to 50% of CRSwNP presenting with comorbid asthma (*Jarvis et al., 2012*) though the contributions of these acute conditions to the development of CRSwNP is not well understood. Asthma has been the most well-defined; approximately 88% of patients with asthma also have radiographic evidence of sino-nasal inflammation and approximately 26 to 48% of patients with asthma also have been diagnosed with CRSwNP. Increased asthma severity has been linked to enhanced sino-nasal inflammation (*Stevens, et al., 2016*).

The close association of CRSwNP with atopic disorders, particularly asthma, has led to a series of clinical studies with biologics that have shown efficacy in asthma. Two anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) and anti-immunoglobulin E (IgE) (omalizumab) have been tested in clinical studies in CRS patients with overall encouraging results (*Chiarella et al., 2017*). More recently dupilumab has also shown to provide benefit to CRSwNP patients (*Pauwels et al., 2015*). These studies have demonstrated the utility of biologics in CRSwNP as a viable option to provide much-needed new therapeutic approaches.

The underlying pathophysiology of CRSwNP is not well-defined. Several factors are thought to contribute to both the development of the disease and complications of treatment. An impaired sino-nasal epithelial barrier could allow for increased exposure to inhaled pathogens and antigens, which, in the setting of a dysregulated host-immune response, could encourage chronic inflammation (*Stevens, et al., 2016*).

Interleukin-33 (IL-33), a tissue-derived cytokine that induces and amplifies eosinophilic inflammation, has emerged as a promising new drug target for asthma and allergic disease (*Smith et al., 2017*). Most recently, IL-33 has been detected in nasal polyps and a series of translational studies have highlighted

the potential central role of IL-33 in the pathogenesis of CRSwNP (*Song et al., 2017*; *Poposki et al., 2017*; *Zhang et al., 2017*). A recent study by Smith et al. resequenced 100 genes that were implicated in asthma to identify a novel sequence variant that directly correlated to eosinophil counts, as well as established asthma loci (IL-33 and IL1RL1) and demonstrated that asthma risk is mediated through IL-33 and eosinophil counts are subsequently reduced, which could reduce the recurrence of nasal polyps following surgery. This study provided a sound rationale for the inhibition of the IL-33 pathway as an effective avenue to contain asthma. Since patients with concurrent CRSwNP and asthma require more sinus surgeries than patients with CRSwNP alone (*Stevens*, *et al., 2016*), a significant clinical need to isolate and inhibit the IL-3 pathway is warranted.

Etokimab is a powerful and efficient inhibitor of IL-33, and thus, etokimab potentially offers an additional and novel treatment approach to treat severe CRSwNP patients who fail to respond to the current therapies.

This Phase 2 study is intended to explore the activity of etokimab in adult subjects with CRSwNP. Etokimab is a highly effective inhibitor of IL-33, a cytokine that is considered to drive the pathogenic cascade in asthma, atopic dermatitis (AD), and CRSwNP. Interleukin-33 directly affects eosinophil counts and function by acting on the early phases of the atopic immune response, which is upstream of current asthma treatments with clinically validated targets such as IL-5, IL-4, and IL-13. The possibility to influence complementary and synergistic pathways involved in CRSwNP pathogenesis may provide a therapeutic improvement compared to the inhibition of single downstream pathways. This study will explore the effects of repeat doses of etokimab, administered subcutaneously (SC), compared to placebo on validated endpoints, such as the Nasal Polyp Score (NPS) and Sino-Nasal Outcome Test (SNOT-22).

2.2 BACKGROUND

2.2.1 BACKGROUND OF DISEASE

The main clinical symptoms observed in CRSwNP are nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. Patients with CRSwNP also report the presence of either anterior or posterior rhinorrhea, along with nasal congestion, hyposmia and/or facial pressure or pain lasting for >12 weeks in duration (*Stevens*, *et al., 2016*). CRSwNP is the most aggressive form of CRS and causes significant morbidity and leads to a diminished quality of life in CRS patients. It is most often diagnosed between 40 and 60 years of age and is more common in males, though females are often found to have a more aggressive disease course than males (*Stevens*, *et al., 2016*). The polyps which occur are detected by a series of instrumental approaches mainly by endoscopy also supported by CT scans.

CRSwNP is the most difficult type of CRS to be satisfactorily treated and often relapses even after surgical treatment. CRSwNP is a common condition observed in up to 5% percent of the US and European population (*Stevens et al., 2016*). Recently, it has been suggested that the severity of CRSwNP is associated with high levels of eosinophils and indeed the presence of eosinophils in tissue or airway

secretions greatly increases the risk of recurrent disease in CRSwNP patients after endoscopic sinus surgery (*Vlaminck et al., 2014*).

Although the pathogenic cascade controlling CRSwNP has not yet been fully elucidated, mounting evidence indicates that CRSwNP shares common pathogenic pathways with asthma, particularly eosinophilic asthma. This is supported by the clinical evidence of CRSwNP severity correlating with eosinophils levels (*Vlaminck et al., 2014*). The close association of CRSwNP with atopic disorders, particularly asthma, has led to a series of clinical studies with biologics that have shown efficacy in asthma. Thus, 2 anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) have been tested in clinical studies in CRS patients (*Chiarella et al., 2017*). Also, anti-IgE (omalizumab) has been tested in these patients with overall encouraging results (*Chiarella et al., 2017*). More recently, dupilumab has also shown to provide benefit to CRS patients (*Paulweis et al., 2015*). All these studies have indicated that the use of biologics in CRSwNP patients is now considered a viable option to provide the much-needed new therapeutic approaches.

Although the pathogenesis of nasal polyps is not fully understood, it is believed that an atopic (Th2) response drives the cascade. Eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps and are frequently associated with asthma and aspirin sensitivity (*Ponikau et al., 2005*). Indeed, the large majority of CRSwNP patients have eosinophilic upper airway inflammation. There is evidence indicating that the magnitude of sinomucosal involvement, polyp size, and severity of nasal disease correlate with the extent of eosinophilic inflammation (*Zacharek, et al, 2003*). Therefore, eosinophils and eosinophilic products are considered the key players of the inflammatory response observed in nasal polyps. In this context, a series of cytokines (ie, IL-5) and mediators (cationic protein, eotaxin) involved in eosinophil activation are elevated in the nasal polyp specimens (*Bhattacharyya et al., 2001*).

Most recently IL-33 has been detected in nasal polyps and a series of translational studies have highlighted the potential central role of IL-33 in the pathogenesis of CRSwNP (*Soyka et al., 2015*; *Lam et al., 2015*). Furthermore, in human subjects with a polymorphism of the IL-33 receptor (ST2), which confers protection from asthma, low levels of eosinophils have been observed in their periphery (*Smith et al., 2017*). Interleukin-33 also potentially activates innate lymphoid cell 2 (ILC2) to release cytokines such as IL-4, IL-13, and IL-5 which amplify the pathogenic Th2 response. Etokimab is a powerful and efficient inhibitor of IL-33, and thus, etokimab potentially offers an additional and novel treatment approach to treat severe CRSwNP patients who fail to respond to the current therapies.

2.2.2 BACKGROUND OF ETOKIMAB

Etokimab (previously known as ANB020) is a first-in-class, anti-IL-33 therapeutic antibody to treat Th2 cell driven inflammatory diseases with underlying IL-33 dysregulation. Etokimab is a humanized immunoglobulin subtype G1/kappa (IgG1/kappa) monoclonal antibody (mAb) that specifically neutralizes the biological effects of human IL-33. Interleukin 33, a member of the IL-1 superfamily (*Pastorelli et al., 2010*) is a multifunctional cytokine that plays an important role in Th2 mediated cellular immunity and in the pathogenesis of atopic diseases (*Liew et al., 2012*; *Nabe et al., 2014*). Etokimab

binds to and inhibits the interaction of IL-33 with its specific cell surface receptor (ST2), thereby, blocking IL-33 driven downstream signaling and subsequent cellular responses. It is being developed for the treatment of atopic diseases such as asthma, AD, and food allergies.

2.2.2.1 NONCLINICAL STUDIES WITH ETOKIMAB

Etokimab is being developed by AnaptysBio Inc. as a lead drug candidate and exhibits strong inhibitory activity for human as well as cynomolgus monkey IL-33. Nonclinical data obtained from studies with etokimab in primary human and cynomolgus monkey cells, and from in vivo nonhuman primate studies demonstrated that:

- Etokimab shows reactivity with human and cynomolgus monkey IL-33 [redacted], but not with mouse or rat IL-33.

- In primary human and cynomolgus monkey cell populations, such as peripheral blood mononuclear cells and human whole blood, etokimab inhibited IL-33 induced interferon gamma (IFN-γ) production. In human basophils, etokimab also inhibited IL-33 induced IL 5 production.

- Etokimab can reduce eosinophilia in mice treated with human IL-33.

- The observed serum apparent terminal half-life ($t_{1/2}$) of etokimab in cynomolgus monkeys was 160 hours after a single intravenous (IV) dose administration, and 187 hours after a single subcutaneous (SC) dose administration at 10 mg/kg, consistent with the anticipated PK characteristics for a human IgG1 scaffold mAb in the monkey.

- Multiple dose, good laboratory practice (GLP)- compliant toxicology and toxicokinetic studies (4-, 13-, and 26-week duration with recovery phase) have been conducted with etokimab administered by SC and intravenous (IV) injection to cynomolgus monkeys. These studies produced no significant test article-related effects, and established a No Observed Adverse Effect Level of [redacted] the highest dose tested.

These data, together with nonclinical safety data generated, support a strong scientific rationale for advancing etokimab into clinical development.

For detailed nonclinical experience with etokimab, refer to the etokimab Investigator's Brochure (IB).

2.2.2.2 CLINICAL STUDIES WITH ETOKIMAB

Currently, clinical findings from 2 completed clinical studies of etokimab (Studies ANB020-001 and ANB020-002) are available and summarized below. Detailed clinical experience with etokimab is provided in the etokimab IB.

2.2.2.2.1 STUDY ANB020-001

Study ANB020-001 was a first-in-human, Phase 1 study in healthy subjects. In the single ascending dose (SAD) phase of the study, 64 healthy subjects were enrolled into 8 treatment arms of 8 subjects each (6 etokimab + 2 placebo per treatment arm). Of these 64 subjects, 24 subjects received etokimab by SC injection (6 each at dose levels of 10, 40, 100, and 300 mg); 24 subjects received etokimab by IV infusion (6 each at dose levels of 40, 100, 300 and 750 mg); 8 subjects received placebo by SC injection; and 8 subjects received placebo by IV infusion. In the single dose portion of the study, etokimab was well tolerated in male and female healthy volunteers, ages 19 to 44 years, when administered a single dose of etokimab of up to 300 mg SC and up to 750 mg IV. A total of 81% of subjects in the placebo group and 79% of subjects in the etokimab group had at least 1 treatment-emergent adverse event (TEAE) during the study. The most commonly reported TEAEs were upper respiratory tract infection (etokimab 48%, placebo 50%), headache (etokimab 27%, placebo 31%), abdominal pain (etokimab 6%, placebo 0%), nausea (etokimab 4%, placebo 0%), vomiting (etokimab 4%, placebo 0%), urticaria (etokimab 4%, placebo 0%), and fatigue (etokimab 4%, placebo 0%).

In the SAD cohort, 1 SAE/SUSAR occurred in a subject who was randomly assigned to etokimab (750 mg) as a single IV injection. The subject developed severe neutropenia (0.2×10^9/L) on Day 22 postdose. The neutrophils level remained clinically significantly low (0.3×10^9/L) on Day 24, but the level returned within normal range by Day 29. No direct role of IL-33 inhibition was noted in this reported SAE of neutropenia.

The multiple ascending dose (MAD) phase of the study, 32 subjects were enrolled into 4 treatment arms of 8 subjects each (6 etokimab + 2 placebo per treatment arm). Of the 32 subjects enrolled, 18 subjects received etokimab by IV infusion (6 each at dose levels of 40, 100, and 300 mg weekly); 6 subjects received etokimab by SC injection (at a dose level of 100 mg weekly); 6 subjects received multiple doses of placebo by IV infusion; and 2 subjects received multiple doses of placebo by SC injection. In the multiple dose portion of the study, etokimab was well tolerated in healthy male and female adult volunteers ages 18 to 45 years, when administered once-weekly for 4 weeks at 100 mg SC and at up to 300 mg as a multiple dose IV. A total of 24 subjects (75%) had at least 1 TEAE, including, 5 of 6 subjects (83%) following SC injection of etokimab, 13 of 18 subjects (72%) following IV infusion of etokimab, and 6 of 8 subjects (75%) following administration of placebo, with a total of 45 TEAEs.

Most adverse events (AEs) were mild in severity (25 of 45 AEs, 56% of all AEs); 19 AEs (42%) were classified as moderate; and 1 AE was classified as severe (2%). Treatment-emergent AEs deemed to be related to study drug administration were reported in 17 of 32 subjects (53%). Of the TEAEs deemed to be related to study drug, 2 AEs were reported in 2 subjects (33%) who received etokimab SC, 14 AEs were reported in 11 subjects (61%) who received etokimab via IV infusion, and 4 AEs were reported in 4 subjects (50%) who received placebo. Of the AEs deemed related to study drug, 8 AEs were mild in severity, 12 AEs were moderate in severity and 1 was considered severe.

The PK data from the study have been utilized to determine route and dose to be used in this study. The PK data generated to date indicate that a linear PK profile is observed upon etokimab administration

regardless of the route. The predicted etokimab half-life is approximately 14 days. Results from the emergent data will serve as basis for the route of administration of Etokimab in future studies.

2.2.2.2.2 STUDY ANB020-002

Study ANB020-002 was a Phase 2a, proof-of-concept, placebo-controlled, open-label study that evaluated the etokimab activity upon house dust mite (HDM) skin challenge in 12 subjects with moderate to severe AD at a single center in the United Kingdom. This study was also conducted to assess the safety and tolerability of Etokimab in subjects with moderate to severe AD.

All 12 subjects included in the safety analysis set experienced at least 1 TEAE during the study. During the placebo period (from Day 1 to Day 8 prior to etokimab administration), 8 (66.7%) subjects experienced at least 1 TEAE and after administration of etokimab (on Day 8), 11 (91.7%) subjects experienced at least 1 TEAE. A total of 10 (83.3%) subjects experienced at least 1 TEAE considered related to etokimab by the Investigator. No severe TEAE was reported, and no subject died during the study. Only 1 (8.3%) subject experienced an SAE (exacerbation of pre-existing depression) after etokimab administration of severe intensity and considered to be unrelated to study drug. None of the subjects discontinued the study due to a TEAE. The most commonly reported TEAEs were dizziness and headache (3 subjects [25%] each) followed by upper respiratory tract infection, urinary tract infection, peripheral swelling, cough, and urticaria (2 subjects [16.7%] each). A total of 10 subjects experienced at least 1 TEAE considered related to etokimab by the Investigator during the study. The most commonly reported treatment-related TEAEs urinary tract infection, and urticaria (2 [16.7%] subjects each).

Anti-drug antibodies titers were low and with no apparent effect on etokimab exposure.

The mean (SD) total Eczema Area and Severity Index (EASI) score decreased statistically significantly after the administration of etokimab. On Day 15, the mean (SD) total EASI score was 19.2 (14.01) and the mean treatment difference from baseline in the total EASI score was -10.8. On Day 22 and Day 36, the mean treatment difference from baseline in the total EASI score was -16.3 (p-value<0.0001) and -17.5 (p-value=0.0008), respectively. The effect of etokimab showed a statistically significant decrease over time in total EASI scores as compared with baseline.

After administration of etokimab (after Day 8 visit), no subject was reported by the Investigator to have an immunoglobulin A (IgA) score of Grade 5 and there was a trend over time for the IgA scores to become less severe. The shift table for the first post etokimab administration assessment on Day 15 showed that 3 (25%) subjects who were Grade 5 at baseline improved to Grade 4; on Day 22, 3 (25%) subjects who were Grade 5 at baseline improved to Grade 4; and on Day 36, 2 (16.7%) subjects who were Grade 5 at baseline improved to Grade 4 and 1 (8.3%) subject who was Grade 5 at baseline improved to Grade 3. At the end of study (EOS) visit, most of the subjects (8 [66.7%] subjects) were Grade 4. Three (25%) subjects who were Grade 5 at baseline improved to Grade 4 at the EOS visit.

The total Scoring Atopic Dermatitis (SCORAD) score decreased statistically significantly after the administration of etokimab. On Day 15, the mean (SD) total SCORAD score was 43.82 (17.753) and the mean treatment difference from baseline in the total SCORAD score was -16.23 (p-value<0.0001). On

Days 22 and 36, the mean treatment difference from baseline in the total SCORAD score was -19.20 (p-value<0.0001) and -21.41 (p-value<0.0001), respectively. The change from baseline of total SCORAD score was statistically significant at all visits post etokimab administration.

The Dermatology Life Quality Index and 5D Itch Scale scores indicated efficacy of etokimab at postdose visits particularly on Days 15, 22, and 36, but with declining efficacy at the later visits.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Etokimab has been extensively tested in animals and there were no etokimab-related adverse findings. The administration of etokimab had no effect on hematology, coagulation, clinical chemistry, or urinalysis test results. Etokimab was found to be safe and well tolerated in a Phase 1 study (ANB020-001) in healthy subjects. There were no deaths during the study. In the Phase 1 SAD study, no change in vital signs (blood pressure [BP], heart rate [HR], electrocardiogram [ECG], or body temperature) were noted. Hematology parameters, such as erythrocyte, white blood cell and platelet counts were all within the normal range except in 1 volunteer in the 750 mg dose group, who reported a serious adverse event (SAE) of neutropenia considered as possibly related to the study treatment. All others did not show any modification or trend related to etokimab dosing.

Serum chemistry results were also all in the normal range. A total of 81% subjects in the placebo group and 79% subjects in the etokimab group had at least 1 TEAE during the study. The most commonly reported TEAEs of mild to moderate intensity included upper respiratory tract infection (50% versus 48% in placebo and etokimab group, respectively) and headache (32% versus 27% in placebo and etokimab group, respectively). No AEs were deemed by the Investigator to be related to etokimab. Of all the AEs reported across all dose groups, 44% were reported as possible related and 36% were reported as unrelated. One SAE of decreased neutrophils was reported in the 750 mg dose group which resolved prior to the study completion with no sequelae. No other observations of decreased neutrophils were observed. No dose-dependent AE presentation was evident.

There were no SAEs in MAD phase of the study. One severe AE of elevated transaminase was reported in the MAD phase of the study. Of the 32 subjects, 24 reported a total of 45 TEAEs; 5 of 6 subjects (83%) following SC administration, 13 of 18 subjects (72%) following IV administration, and 6 of 8 subjects (75%) following placebo administration. Most of the AEs were mild in severity (25 of 45 [56%] subjects), 19 (42%) AEs were considered moderate and 1 AE was classified as severe AE (2%). Of the 32 subjects, 17 subjects (53%) reported TEAEs considered related to the study drug. Of these, 2 AEs were reported in 2 subjects (33%) who received etokimab via IV infusion and 4 AEs were reported in 4 subjects who received placebo. The most commonly reported AEs were headache, upper respiratory tract infection, and abdominal pain.

Although there is no evidence to date for an allergic or immunologic reaction to etokimab, such a reaction to any drug is possible. Symptoms of allergic reactions can include rash, wheezing or difficulty

breathing, dizziness or fainting (also a possible outcome of a drop in BP), swelling around the mouth, throat or eyes, a fast HR, or sweating.

Based on clinical studies with other mAbs, subjects in this mAb study may experience symptoms of an immune reaction to the drug, also known as 'cytokine release syndrome.' These symptoms of this vary dramatically but can include:

- Mild to moderate fever, chills, headache, nausea, and vomiting.
- Moderate to severe symptoms such as edema (swelling of the skin), hypotension (low BP), and pulmonary infiltrates (eg, blood and mucus in the lung).

Details about specific risks for subjects in this clinical trial can be found in the etokimab IB and ICF.

2.3.2 KNOWN POTENTIAL BENEFITS

A subject with CRSwNP may or may not receive direct benefit from participating in this study. Details about specific benefits for subjects in this clinical study are provided in the etokimab IB and ICF.

Based upon the inhibition of IL-33 by the study drug and preclinical study and early Phase 2, results, subjects with CRSwNP who are randomized to active treatment may benefit from treatment with etokimab. Participation in this study may help develop important scientific knowledge that could contribute to the development of a new novel medication to be used in the treatment of subjects who suffer from AD, asthma, and food allergies.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In clinical development to date, etokimab (administered by SC or IV) has been shown to be generally well tolerated at all dose levels without any systemic or local safety concerns.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To evaluate the efficacy of etokimab compared to placebo in the treatment of subjects with CRSwNP following a 16-week treatment period	• Change from baseline to Week 16 in bilateral endoscopic NPS • Change from baseline to Week 16 in Sino-Nasal Outcome Test (SNOT-22) scores	Change in NPS and SNOT-22 are outcome measures that have been established as clinically relevant for assessing treatment response to mAbs for the management of CRSwNP symptoms
Secondary		
• To evaluate the effectiveness of etokimab compared to placebo in subjects with CRSwNP in relieving clinical symptoms	• Time to first response (≥ 1 point improvement) in NPS • Responder analysis: response defined as a reduction of at least 1 point from baseline to Week 16 in NPS • Responder analysis: response defined as a reduction of at least 12 points from baseline to Week 16 in SNOT-22 • Change from baseline to Week 16 in sense of smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT)	These endpoints are outcome measures that have been established as clinically relevant for assessing treatment response of mAbs for the management of CRSwNP symptoms
• To assess the safety and tolerability of etokimab in subjects with CRSwNP compared to placebo following a 16-week treatment period	• Incidence of AEs and TEAEs • Incidence of SAEs • Changes in clinical laboratory tests (hematology, chemistry, and urinalysis) • Changes in vital signs (BP, temperature, respiration rate, and pulse rate) • Changes in ECG parameters • Immunogenicity (ADA and neutralizing ADA)	These endpoints are outcome measures that have been established as clinically relevant for assessing the safety and tolerability of mAbs for the management of CRSwNP symptoms
• To assess the pharmacokinetics (PK) of etokimab in human serum in subjects with CRSwNP following subcutaneous (SC) administration	• CL/F • Apparent volume of distribution • C_{max} • Time of maximum concentration (t_{max})	These PK endpoints are PK-specific outcome measures that have been established as clinically relevant for assessing the PK of mAbs for the

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{tau}) • Apparent terminal half-life ($t_{1/2}$) will also be determined for etokimab after SC administrations, as possible	management of CRSwNP symptoms
Exploratory		
• To assess improvement in Quality of Life (QoL) in subjects with CRSwNP treated with etokimab compared to placebo following a 16-week treatment period	• QoL: ○ 36-item Short Form Health Survey (SF-36) ○ European QoL scale (EQ-5D) ○ Patient-related rhinosinusitis symptoms severity using a visual analogue scale (VAS) ○ Number of nocturnal awakenings	To assess the effect of etokimab on the patients' symptoms and quality of life
• To assess other effects of etokimab compared to placebo in subjects with CRSwNP following a 16-week treatment period	• Percent change from baseline to Week 16 in sinus opacification as assessed by CT scan using Lund-Mackay score • Change from baseline to Week 16 in nasal peak inspiratory flow (NPIF) • Change from baseline to Week 16 in NPS in subjects with comorbid asthma • Change from baseline to Week 16 in Sino-Nasal Outcome Test (SNOT-22) scores in subjects with comorbid asthma • Percent change from baseline to Week 16 in 3-dimensional volumetric measurement of the maxillary sinus as assessed by CT scan • Change from baseline to Week 16 in forced expiratory volume (FEV_1) (overall and in subgroup with asthma) • Change from baseline to Week 16 in FEV_1 percent of predicted (overall and in subgroup with asthma) • 7-Item Asthma Control Questionnaire (ACQ-7) in asthma subgroup • Reduction of eosinophils (blood eosinophil count) from baseline (Day 1 pre-dose) to Week 16	All other efficacy endpoints have been re-categorized as exploratory endpoints Additional measures of treatment response are established methods to characterize the clinical impact of treatment Patient-reported outcomes specific to CRSwNP provide additional evidence to support the physician assessment of outcome

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Time to study treatment discontinuation • Incidence of treatment discontinuation due to need for oral corticosteroids (OCS) or nasal polyp surgery • Change in Nasal Polyp Resource Questionnaire from baseline to Week 16	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multiple dose, Phase 2 study designed to assess efficacy, safety, tolerability, and PK of 2 different doses and dose regimens of etokimab following a 16-week treatment period compared to placebo in adults with moderate to severe CRSwNP. The total study duration will be approximately 28 weeks.

A Sponsor-designated centralized reader will be used to confirm the diagnosis of CRSwNP as assessed by nasal endoscopy, CT scan of sinuses, and symptom scoring to reduce the risk of interpretation variation.

This study has 3 periods: a 4-week screening period (maximum of 31 days), with a minimum MFNS run-in of 20 days prior to the administration of study drug on Day 1; a 16-week treatment period (Week 0 to Week 16); and an 8-week safety follow-up period.

During the screening period, all subjects will undergo evaluation for eligibility. Subjects will be randomly assigned on Day 1 to one of the following 3 treatment arms in a 1:1:1 ratio:

- Etokimab 300 mg load + 150 mg SC every 4 weeks (Weeks 0, 4, 8, and 12)
- Etokimab 300 mg load + 150 mg SC every 8 weeks (Weeks 0 and 8) and placebo (Weeks 4 and 12)
- Placebo (Weeks 0, 4, 8, and 12)

Eligible subjects will be administered study drug SC during onsite visits on Day 1 (Week 0), Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12). Subjects will remain onsite for 2 hours for post-dose observation following the initial (Week 0/Day1) study drug injection. Additional visits will occur on Day 5 (Week 1) and Day 113 (Week 16) during the treatment period. During the safety follow-up period, subjects will return to the study center on Day 141 (Week 20) and Day 169 (Week 24) EOS (see Section 1.3).

Subjects will also be provided MFNS for use during the trial and are required to undergo a minimum run-in period of 20 days prior to Day 1 with approximately 80% compliance. Subjects will use MFNS of 2 actuations (50 µg/actuation) in each alternate nostril twice daily (BID), total daily dose of 400 µg,

throughout the study, unless they are intolerant to BID intranasal corticosteroids (INCS) in which case, subjects can stay on the lower dose regimen of 1 actuation (50 µg/actuation) in each nostril BID, total daily dose of 200 µg, additional decreases should be discussed with the Medical Monitor. If physician lowers dose regimen due to intolerance, compliance will be based on lower dose. Any changes to the MFNS must be documented and recorded in eCRF.

Serum samples for PK and immunogenicity will be collected before the administration of study drug and at the other time points specified in the SOA (see Section 1.3).

Safety assessments including AE/SAE monitoring, vital signs, physical examinations, ECGs, and laboratory measurements will be performed as specified in the SOA (see Section 1.3).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This Phase 2 study will explore the activity of etokimab in adult subjects with moderate to severe CRSwNP. Etokimab is a highly effective inhibitor of IL-33, a cytokine that is considered to drive the pathogenic cascade in asthma, AD, and CRSwNP. Interleukin-33 directly affects eosinophil counts and function by acting on the early phases of the atopic immune response, which is upstream of current asthma treatments with clinically validated targets such as IL-5, IL-4, and IL-13. The possibility to influence complementary and synergistic pathways involved in CRSwNP pathogenesis may provide a therapeutic improvement compared to the inhibition of single downstream pathways. This study will explore the effects of repeat doses of etokimab, administered SC over a 16-week treatment period, compared to placebo on validated endpoints, such as the NPS and SNOT-22.

4.3 JUSTIFICATION FOR DOSE

Data from the etokimab Phase 1 (ANB020-001) and Phase 2a (ANB020-002) studies are the basis for the selection of the dose of etokimab for the current study. The dose range of etokimab selected for this study has been used safely in study ANB020-001. Etokimab pharmacodynamic activity, measured as inhibition of ex-vivo IL-33 stimulated INF-γ production, can be inferred from the correlation with PK data. All of the selected dose levels of etokimab are predicted to induce full IL-33 inhibition within 2 days for at least 9 to 10 days after dosing. The administration of etokimab loading doses will allow systemic concentrations to reach serum concentrations sustaining more than 95% IL-33 inhibition faster, potentially reducing the time to onset of clinical effect. Data from the Phase 2a study show a clinical response 1 week after etokimab administration (300 mg IV), and the dose was found to be safe and well tolerated. One month after etokimab administration, the average EASI score reduction was 61% and the average pruritus reduction was 32% relative to baseline. Sustained clinical response was observed after 2 months after etokimab administration.

4.4 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all scheduled study visits, including the last visit or the last scheduled procedure, as shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as the date of the last visit or procedure of the last subject in the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Male or female, aged 18 to 70 years at the time of consent.
2. Present with a minimum bilateral total NPS of 4 out of 8 (maximum score), with minimum score of 1 in each nostril, despite completion of a prior INCS treatment at least 8 weeks before Screening.
3. Present with at least 2 of the following symptoms prior to Screening:
    a. Nasal blockade/obstruction
    b. Nasal congestion
    c. Nasal discharge (anterior/posterior nasal drip)
    d. Facial pain/pressure, and
    e. Reduction in or loss of smell
4. Body mass index (BMI) of 18 to 42 kg/m^2 (inclusive) and total body weight > 50 kg (110 lb).
5. Agrees to the following conditions regarding contraception and pregnancy:
    a. A male subject must agree to use contraception as detailed in the protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.
    b. A female subject of child bearing potential must have a negative serum pregnancy test (β-human chorionic gonadotropin) at Screening and a negative urine pregnancy test at Baseline (Day 1), is not lactating, and at least one of the following conditions applies:
        i. Not a WOCBP as defined in the protocol, OR
        ii. A WOCBP who agrees to follow the contraceptive guidance in the protocol during the treatment period and for at least 3 months after receiving the last dose of study treatment. The female subject's selected form of contraception must be effective by the time the female subject enters into the study (eg, hormonal contraception should be initiated at least 28 days before Day 1).
6. Screening laboratory values must meet the following criteria:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq$ 3 x ULN
    b. Total bilirubin $\leq$ 1.5 x ULN
    c. Albumin $\geq$ 3 g/dL - lipase $\leq$ 1.5 ULN (if collected)

    If a subject has liver function tests (LFTs) within normal and defined limits at Screening and meets all other inclusion criteria at Screening and baseline, the subject can be dosed.

7. Capable of giving signed informed consent and understanding the requirements and restrictions listed in the ICF.

8. Subject must use MFNS as provided by the Sponsor and be approximately 80% compliant during the screening period through Day 1.

9. Willing to and capable of complying with the study protocol requirements.

10. Able to read and to understand the study procedures and have the ability to communicate meaningfully with the Investigator and staff.

11. Confirmation of completion of 1 week of daily NPIF recordings (twice daily) on Day 1, prior to randomization. (A minimum of approximately 5 days must be completed of the 7 consecutive days requested).

5.2 EXCLUSION CRITERIA

Subjects are excluded from the study if any of the following criteria apply:

1. Prior exposure to etokimab.

2. SNOT-22 score $\leq$ 15 at Screening.

3. Use of other investigational drugs or prohibited therapy for this study within 8 weeks before screening or 5 half-lives, whichever is longer:

    a) Have required an increase of OCS or INCS drops within the 2 months before screening or are scheduled to receive OCS during the study period for another condition

    b) Have undergone any previous monoclonal antibody (mAb) or immunosuppressive treatment

    c) Leukotriene antagonists/modifiers for subjects who were not on a continuous treatment for $\geq$ 30 days prior to Screening

4. Have a documented history of aspirin-exacerbated respiratory disease (AERD) diagnosis as confirmed by a medical provider with an oral aspirin challenge.

5. Have concomitant medical condition(s) that may interfere with the Investigator's ability to evaluate the subject's response to the investigational product (IP).

6. Have experienced a severe life-threatening anaphylactic reaction to human, humanized, chimeric, or murine monoclonal antibodies.

7. Have participated in any interventional study for the treatment of CRSwNP in the 3 months before Screening.

8. Have received high dose systemic corticosteroids (equivalent to > 15 mg/day prednisone), prolonged nonsteroidal, immunosuppressant, or immunomodulating treatments within 8 weeks before Screening.

9. Have received treatment with biologics such as dupilumab, mepolizumab, or omalizumab within 12 weeks or 5 half-lives (5 $T_{1/2}$), whichever is longer, before Screening.

10. Clinically significant abnormal ECG assessment at Screening (any abnormality that the Investigator believes is not safe for study participation).

11. History of ischemic cardiovascular disease(s) or cerebrovascular event within 1 year of Screening.

12. Have received any systemic antibiotic treatment within 4 weeks before Screening.

13. Have a history of hypersensitivity or allergic reactions to [redacted] a component of the etokimab formulation or the inactive ingredients (excipients).

14. If female, is pregnant or lactating, or intends to become pregnant during the study period.

15. Current smokers or former smokers with a smoking history of ≥10 pack-years [(number of cigarettes per day/20) × number of years smoked]. A former smoker is defined as a subject who quit smoking at least 2 months prior to screening visit. This includes electronic cigarettes and vaping. Subjects who smoke medicinal marijuana can be enrolled at the Investigator's discretion (conversion to edible forms of marijuana is preferred). Occasional smoking is permitted at the discretion of the Investigator (eg, cigar or pipe for significant event, occasional/rare weekend cigarette or marijuana use).

16. Positive blood screen for hepatitis C virus antibody, hepatitis B virus core antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV) 1 and 2 antibodies (except subjects who test positive for hepatitis B surface antigen alone due to a hepatitis B vaccination).

17. Presence of chronic or active infection at Screening including positive result for active tuberculosis (TB) (ie positive QuantiFERON® test result without any prior history of active nor latent TB infection and without evidence of active infection) where the subject has not completed prophylactic treatment.

18. Any comorbidity that the Investigator believes is a contraindication to study participation. This includes, but is not limited to, any respiratory (eg, pulmonary fibrosis, eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis), cardiovascular, gastrointestinal, hematological, neurological, immunological, musculoskeletal, renal, infectious, neoplastic, or inflammatory condition that may place the safety of the subject at risk during the study, impact results of the study or their interpretation, or prevent subject from completing the study.

19. Comorbid asthma when:

    a) Forced expiratory volume (FEV_1) ≤60% of predicted normal as assessed on Day 1 as defined by the Global Lung Initiative (GLI)

    b) An exacerbation requiring systemic (oral and/or parenteral) corticosteroid treatment or hospitalization (> 24 hours) for treatment of asthma within 3 months prior to Screening

    c) A daily dose higher than 1000 μg fluticasone or the equivalent of inhaled corticosteroids

20. Have any other physical, mental, or medical conditions that, in the opinion of the Investigator, makes study participation inadvisable or could confound study assessments.
21. Receipt of live attenuated vaccine within 4 weeks before Screening.
22. Planned surgery during the study or within 30 days before Screening.
23. History of malignancy within 5 years, except non-melanoma skin cancer that has been fully treated with no current active disease.
24. Initiation of allergen immunotherapy:
    a) Within 12 weeks prior to Screening
    b) Planned to begin therapy during the screening period
    c) Planned to begin during the randomized treatment period

    Subjects who started immunotherapy more than 12 weeks prior to Screening can continue the immunotherapy during the study providing dosing is at least 2 weeks prior to each dose of study drug.
25. Undergone any nasal surgery (eg, any procedure with excision of tissue) within 3 months before randomization (Day 1).
26. Evidence of drug/substance abuse that would pose a risk to subject safety, interfere with the conduct of the study, or affect the subject's ability to participate in or comply with the study protocol, including but not limited to evidence of misuse of addictive drugs, such as opioids, outside of prescribed medications for a medical condition.

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened up to 2 more times during the enrollment period of the study. All requests for second rescreening must be discussed with the medical monitor and approved by the Sponsor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention plan for this study will be provided in a separate Manual of Procedures (MOP).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Etokimab protein drug substance (DS) was produced using a conventional monoclonal antibody manufacturing process. Etokimab drug product (DP) was produced by sterile filtration and aseptic fill of drug substance into glass vials, without additional processing. The container closure system for the DP is a 2Rtype I glass vial with 13 mm chlorobutyl stoppers and 13 mm aluminum seals. Multiple DP lots may originate from a single DS lot.

The identically matched placebo used in this study contains no active drug product.

6.1.2 DOSING AND ADMINISTRATION

Eligible subjects will be randomly assigned on Day 1 to 1 of 3 treatment arms in a 1:1:1 ratio:

- Etokimab 300 mg load + 150 mg SC every 4 weeks (Weeks 0, 4, 8, and 12)
- Etokimab 300 mg load + 150 mg SC every 8 weeks (Weeks 0 and 8) and placebo (Weeks 4 and 12)
- Placebo (Weeks 0, 4, 8, and 12)

Study drug will be administered SC during onsite visits on Day 1 (Week 0), Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

Subcutaneous injection sites should be alternated among upper arms or, if necessary, the different quadrants of the abdomen (avoiding navel and waist areas). If possible, the same site should not be injected for 2 consecutive months. Study drug should be administered only into areas of normal-looking skin; if possible, Day 1 (loading dose) injections should be administered in separate upper arms. If both injections are administered in the same area, the injections should be spaced approximately 2 inches apart. Additional detail will be located in the Pharmacy Manual.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study centers are required to actively acknowledge receipt of shipment of IP and confirm that appropriate refrigeration was maintained during transit through accessing the temperature monitoring device(s) with each shipment. The Pharmacy Manual should be referred to for additional information and details.

6.2.2 ETOKIMAB FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Etokimab is a sterile, colorless to slightly yellowish solution that is formulated at [redacted] Each single-use vial contains [redacted] of solution and [redacted] of etokimab.

Identically matched placebo is supplied as a solution in single-use vials that contain active drug product.

All IP vials will be packaged and labeled in accordance with all applicable laws and regulations.

6.2.3 ETOKIMAB STORAGE AND STABILITY

Etokimab or placebo vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. Etokimab or placebo should not be used beyond the retest or expiration date provided by the manufacturer. Vial contents should not be frozen or shaken. Etokimab or placebo may be stored at room temperature (> 8°C to 25°C [46°F to 77°F]) in the undiluted and/or diluted state for a maximum of 8 hours. Vials are intended for single-use only; therefore, any remaining solution should be discarded. Compatibility testing has shown that etokimab is stable and does not adsorb to the polyethylene or polypropylene syringes or standard hypodermic needles.

6.2.4 INVESTIGATIONAL PRODUCT PREPARATION

Investigational product (study drug or placebo) will be prepared by a trained dose preparer. Dose preparation records will be completed and securely maintained by the dose preparer. Both etokimab and placebo have the same appearance in the syringe, thereby ensuring that the study team and subjects will remain blinded to study treatment. Syringes of etokimab and placebo will be prepared based on treatment group assignment.

6.2.5 INVESTIGATIONAL PRODUCT DOSING INSTRUCTIONS

Dosing instructions for study drug (etokimab and placebo) will be provided in the Pharmacy Manual. Injections of study drug will be administered following clinic procedures and blood collection at scheduled visits during the randomized treatment period (see SoA, Section 1.3).

Subjects will be monitored for 2 hours by the Investigator or study personnel after the initial (Week 0/Day 1) injection of study drug, for any signs or symptoms of a local site injection or

hypersensitivity reaction. Subjects with any ongoing treatment-emergent AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant. Subjects are not required to remain onsite after follow-up injections (Weeks 4, 8, and 12) unless deemed necessary by the Investigator, if there have been injection site reactions, or other AEs are noted.

6.2.6 MOMETASONE FUROATE NASAL SPRAY FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Mometasone furoate, the active component of MFNS, 50 µg, is an anti-inflammatory corticosteroid having the chemical name, 9,21-Dichloro-11ß,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione17-(2 furoate).

Mometasone furoate is a white to off-white powder, with a molecular formula of C_{27} H_{30} C_{12} O_6 and a molecular weight of 521.43 g/mol. It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone and chloroform; and freely soluble in tetrahydrofuran. Its partition coefficient between octanol and water is >5000.

Mometasone furoate nasal spray 50 µg is a metered-dose, manual pump spray unit containing an aqueous suspension of 0.05% w/w mometasone furoate in an aqueous medium containing benzalkonium chloride, citric acid, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80 and sodium citrate. The pH is between 4.3 and 4.9. Each bottle contains 120 metered sprays.

6.2.7 MOMETASONE FUROATE NASAL SPRAY FORMULATION-DOSING INSTRUCTIONS

Subjects will also be provided MFNS for use during the trial. Subjects will use MFNS of 2 actuations (50 µg/actuation) in each nostril twice daily (BID), total daily dose of 400 µg, throughout the study, unless they are intolerant to BID INCS in which case, subjects can stay on the lower dose regimen of 1 actuation (50 µg/actuation) in each nostril twice daily (BID), total daily dose of 200 µg, additional decreases should be discussed with the Medical Monitor.

If the Investigator lowers the dose regimen due to intolerance, compliance will be based on lower dose. Any changes to the MFNS must be documented and recorded in eCRF.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 RANDOMIZATION

This is a randomized, double-blind, placebo-controlled, parallel-group study with limited access to the randomization code. All subjects will be centrally assigned to randomized study treatment using an Interactive Web Response System (IXRS). As subjects become eligible, they will be assigned sequential

randomization numbers which will be used to assign the allocated treatment based on a randomization schedule. Before the study is initiated, the telephone number and call-in directions for the IXRS and/or the log in information and directions for the IXRS will be provided to each study center. Study treatment will be prepared and dispensed at the study visits by a pharmacist or designee as summarized in Section 6.2.4 and the Pharmacy Manual; the visits at which this will occur are summarized in the SoA (Section 1.3).

Eligible subjects will be randomized on Day 1 to 1 of 3 treatment arms in a 1:1:1 ratio (see Section 6.1.2), based on a computer-generated randomization schedule prepared by or under the supervision of the Sponsor. The randomization will be stratified by asthma comorbidity. The IXRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The pharmacist or designee will not be aware of treatment assignment (etokimab or placebo) and will be provided only kit numbers to assign study drug.

All calls resulting in an unblinding event are recorded and reported by the IXRS. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind without informing the Sponsor of the treatment assignment. The date and reason that the blind was broken, but not the treatment assignment, must be recorded in the source documentation eCRF, as applicable.

The assessments of efficacy will be performed by the Investigator or qualified designee, who is blinded to the subject's treatment group assignment. When all of the study data have been entered into the study database and verified, the randomization code will be broken for data analysis.

6.3.2 BLINDING

Under normal circumstances, the blind should not be broken until all subjects have completed the double-blind phase of study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment the subject is receiving. In such cases, the Investigator may in an emergency determine the identity of the treatment by IXRS. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week.

The IXRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject's safety must always be the first consideration in making such a determination and unblinding should be performed only if the subject's well-being requires knowledge of the subject's treatment assignment, or if requested by the Data Safety Monitoring Board (DSMB).

In the event the blind is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the Investigator in the appropriate section of the eCRF, and in the source document. The documentation received from the Interactive Web Response System indicating the code break must be retained with the subject's source documents in a secure manner (eg, sealed envelope) so as not to unblind the treatment assignment to the study site,

Sponsor/contract research organization personnel. The Investigator is also advised not to reveal the study treatment assignment to the study site or Sponsor personnel.

6.4 STUDY INTERVENTION COMPLIANCE

The assigned dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be captured in the eCRFs and will be recorded as a protocol deviation.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and supplements.

Any medication, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment and during the study must be recorded on the eCRF.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of prohibited medications is provided in Appendix A.

6.5.1 RESCUE MEDICINE

Use of rescue medication (eg, systemic corticosteroid) is not permitted in this study (except MFNS as supplied per protocol). If a subject receives systemic rescue treatment the subject will be discontinued from the study and should return for a final Early Termination Visit (ETV) within 30 days from last dose. Study procedures should be completed according to the ETV/EOS per Section 1.3. In the case of ongoing AEs/SAEs, the subject should be followed up until it has resolved or stable outcome or subject is lost to follow-up. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded into the eCRF/study database by study center personnel.

6.6 DOSE MODIFICATION

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the Investigator's discretion. Any interruption should be discussed with the medical monitor in advance but no later than 24 hours after it has occurred.

6.7 TREATMENT AFTER THE END OF THE STUDY

All subjects will return to the study center for the EOS (Day 169) or ETV for final safety and EOS assessments. After this visit, subjects should be treated according to the Investigator's clinical judgment. Care after EOS/ETV will not be provided by the Sponsor. Any AE which in the opinion of the Investigator

is related to the study drug, SAE, or pregnancy occurring within 30 days after the EOS visit should be reported to the medical monitor and followed up until it has resolved or stable outcome or subject is lost to follow-up.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Study treatment can be interrupted temporarily in case of an AE as per the Investigator's discretion. The medical monitor should be informed. Restarting study treatment at the next scheduled administration study visits can be done after discussion with the medical monitor.

In the case of discontinuation from study treatment the subject should return for an ETV within 30 days from last dose and will be encouraged to complete their remaining clinic visits as planned. Study procedures should be completed according to the (ETV)/(EOV) per Section 1.3. Ongoing AEs/SAEs, the patient should be followed up until it has resolved or stable outcome or subject is lost to follow-up.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

In case of early withdrawal from the study, the subject will be required to return as noted above for ETV. Procedures should be completed in accordance with the SoA (see Section 1.3) Week 24/ETV.

If an ETV occurs within 7 days of the previous visit lab re-draws are not required unless clinically significant labs were noted.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

An Investigator must discontinue or withdraw a subject from the study and follow for safety for the following reasons:

- Any subject becomes pregnant or indicates they are planning to become pregnant during the study
- Any LFT abnormality that meets the following criteria require discontinuation:
  - If a subject has at any time post-initial dose an AST or ALT >5-8x ULN for more than 2 weeks, discontinue dosing; or
  - AST or ALT >8x ULN, irrespective of duration discontinue dosing; or
  - Concurrent AST or ALT >3x ULN and total bilirubin >2x ULN discontinue dosing.

An Investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention noncompliance (eg, failure to follow study procedures or to keep follow-up appointments)
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression which requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

If the subject withdraws consent and discontinues from the study, the Investigator will attempt to determine the reason for discontinuation and record the reason in the subject's study records and on the eCRF. If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, the subject should be asked to return to the study center to complete the assessments specified in the ETV.

If at any time during the study, the investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject at any time if medically necessary. Appropriate documentation in the subject's study record and eCRF regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the Investigator will discuss his/her intentions with the medical monitor or designee.

All subjects who fail to return to the study center for the required follow-up visits will be contacted by phone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a minimum of 2 documented attempts (one attempt on 2 different days), a registered letter will be sent requesting that contact be made with the Investigator.

The Sponsor has the right to terminate or to stop the study at any time. Should this be necessary, both the Sponsor and the Investigator will ensure that proper study discontinuation procedures are completed.

Subjects who sign the ICF and are randomized but do not receive the study intervention may be replaced. Subjects who sign the ICF, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

Study center personnel will attempt to contact the subject and reschedule any missed visit as soon as possible, if it does not fall within the next visit's window, and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study. If the re-scheduled visit falls within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned.

Missed visits must be captured in the eCRFs and will be recorded as a protocol deviation.

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

As part of study preparations, Investigators will receive standardized training on the efficacy assessments in this study. The same Investigator will perform all efficacy assessments for a given subject, as practical given the long study follow-up duration.

8.1.1 NASAL ENDOSCOPY AND NASAL POLYP SCORE

Nasal endoscopy is one of the co-primary endpoints in the study (ie, change in NPS from baseline to Week 16). It will be performed according to the SoA (see Section 1.3), if the endoscopy is performed onsite during the study visit, it should occur after study assessments (eg, QoL assessments, labs, UPSIT, etc.) have been completed and preceded by local administration of anesthetic drugs in combination with a decongestant. The nasal endoscopy must be performed prior to dosing on Day 1, Week 4, Week 8, and Week 12. The Day 1 endoscopy can be scheduled up to 5 days prior to the Day 1 visit; visit windows can be utilized for scheduling follow-up nasal endoscopies. For the analysis of primary endpoint, central reading of Day 1 will be used for comparison with central reading at Week 16. The sites will remove subject-identifying information from the imaging data header and label with subject ID prior to sending the imaging data to the central reader.

Standard video sequences of the nasal endoscopy will be downloaded or sent to a Sponsor-designated centralized reader at the completion of the visit for adjudication. Nasal endoscopy will be performed using centralized imaging data assessments and scoring by an independent reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at Study Day 1, only the screening visit pass/fail results will be made available to the study center. The final results of central reading will be made available after the study.

Further details on nasal endoscopy will be available in a separate operational manual provided to the sites.

A sample NPS is provided in Appendix D.

8.1.2 SINO-NASAL OUTCOME TEST (SNOT-22)

The SNOT-22 is one of the co-primary endpoints of the study (ie, change in SNOT-22 from baseline to Week 16). It is a 22-item outcome measure on a 5-category scale applicable to sino-nasal conditions and surgical treatments. The score ranges from 0 to 110. Higher total scores on the SNOT-22 imply greater impact of CRS on QoL. The questionnaire was found easy to use (time to completion is approximately 7 minutes) and provided good discriminant validity (*Hopkins et al., 2009*). The SNOT-22 was validated and recommended for routine clinical practice. A Minimal Clinically Important Difference MCID is available: ≥ 8.90 (*Chowdhury et al., 2017*; *Steele et al., 2016*; and *Rudmik et al., 2015*).

The SNOT-22 will be completed as indicated in the SoA (see Section 1.3) and is located on the clinical tablet. This frequent SNOT-22 might provide a kinetic profile of etokimab efficacy in subjects with CRSwNP.

A sample SNOT-22 is provided in Appendix E.

8.1.3 NASAL PEAK INSPIRATORY FLOW

Nasal peak flow evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration and/or expiration expressed in liter per minute. The NPIF is the best validated technique for the evaluation of nasal flow through the nose. Nasal inspiration correlates most with the subjective feeling of obstruction and is the best validated technique for monitoring nasal flow in clinical trials.

Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of expression of the result (*Juniper et al., 2004*). All 3 values will be recorded by the subject in the diary, and the highest value will be used for evaluation. The procedure takes about 5 minutes. Baseline AM NPIF will be the mean AM measurement recorded for 7 consecutive days or 1 week during the screening period, prior to the first dose of IP, and baseline PM NPIF will be the mean PM measurement recorded for 7 consecutive days or 1 week during the screening period, and prior to the first dose of IP. Baseline will be the mean, averaged measurement from the 7-day period.

At Screening (Visit 1), subjects will be issued an NPIF meter for recording morning (AM) and evening (PM) NPIF. Subjects will record values twice a day for 7 consecutive days during the screening period, and twice a day, every day throughout the treatment and safety follow-up period (Weeks 0-24), according to diary instructions. Subjects will be instructed on the use of the meter, and written instructions on the use of the NPIF meter will be provided to the subjects. In addition, the Investigator will instruct the subjects on how to record the following variables in the diary on a daily basis.

- AM NPIF should be performed approximately 15 minutes after arising prior to taking MFNS
- PM NPIF should be performed in the evening prior to taking MNFS

Three NPIF efforts will be performed by the subject and recorded.

During the screening period NPIF recording will be collected on a paper diary provided to subjects. Subjects must return the paper diary to the site on Day 1. Subjects should complete the diary twice a day for 7 consecutive days during the screening window; however, at least 5 of the 7 days must be completed during the screening period to be eligible for enrollment.

At Day 1 subjects will be provided an eDiary to collect NPIF recordings throughout the remainder of the trial. Diary compliance must be approximately 80% throughout the study duration.

8.1.4 UNIVERSITY OF PENNSYLVANIA SMELL IDENTIFICATION TEST

The UPSIT is a rapid and easy-to-administer method to quantitatively assess human olfactory function. It shows a high test-retest reliability (r: 0.981) and scores on this test are strongly correlated with the detection threshold for phenyl ethyl alcohol in the same individuals. When the UPSIT is administered in the standardized manner, clinical subjects show a high degree of uniformity in UPSIT performance when tested in different laboratories.

The 40-odorant UPSIT is used in over 1500 clinics and laboratories throughout the US, Canada, South America, and Europe, and has been administered to nearly 200,000 people since its development in the early 1980s. A particular strength of this test is that it provides an olfactory diagnosis based on comparing the subject's test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish subjects with a normal sense of smell ("normosmia") from those with different levels of reduction ("mild, moderate and severe microsmia") or loss ("anosmia") (*Juniper et al., 2004*).

8.1.5 DISEASE-SPECIFIC TESTS AND ASSESSMENTS

Computed tomography of the sinuses should be performed at Day 1 (Week 0) and at Day 113 (Week 16/EOT). Day 1 CT must be collected prior to dosing on Day 1. If necessary, the Day 1 CT can be collected prior to Day 1, however all efforts should be made to conduct CT after subject screening labs have been reviewed and it is determined subject is likely eligible for the study. Any CTs collected within 3 months of Visit 2 (Week 0) can be used for in lieu of a new CT at Day 1.

For both Lund-Mackay scores and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent reviewer. Central reading of Visit 2 will be used for comparison with EOT. The final results of central reading will be made available after the study. Details on CTs will be available in a separate operational manual provided to the sites.

8.1.5.1 LUND-MACKAY SCORE

Lund-Mackay system is based on localization with points given for degree of opacification:
0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal

complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side (*Lund and MacKay, 1993*). This scoring system has been validated in several studies (*Metson et al., 1997*; *Oluwole et al., 1996*). For patients in whom the osteomeatal complex (OC) is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

8.1.5.2 3-DIMENSIONAL VOLUMETRIC MEASUREMENT OF THE MAXILLARY SINUS

This method is used to calculate: (*Deeb et al., 2011*)

- the volume of the air (mL)
- the volume of mucosa (mL)
- % occupied by disease
- thickness of lateral wall

For the analysis, central reading before V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader. The percent change in opacification from baseline to EOT will be calculated.

8.1.6 POLYP BIOPSIES

Study centers with the capability to perform a nasal polyp biopsy and with consent of the subject, will collect samples as noted below.

A baseline biopsy will be obtained at Day 1 (Week 0) of the study (before injection of the study drug). After randomization, another biopsy of nasal polyp tissue will be obtained at Week 16.

The complete details on tissue collection and processing will be provided separately. Briefly, the biopsied polyp tissue will be weighed (mg) and then cut into cubes of approximately 0.5 cm in each dimension. All but one cube will be individually placed into labeled cryotubes and immediately frozen with liquid nitrogen, and then maintained at -70°C or colder until shipped on dry ice to a central storage site or laboratory. Nasal polyp tissue will be subsequently assessed for various biomarkers of inflammation and disease process or response. Any remaining tissue will be discarded within 5 years of the completion of the last visit for the last patient in the study. Additional information on collection, processing, storage, and shipment of samples is located in the laboratory manual.

8.1.7 WHOLE BLOOD SAMPLING AND DNA SAMPLING

For those subjects who consent to whole blood RNA and DNA sampling, blood samples will be collected at timepoints as indicated in the SoA (Section 1.3) and sent to the central laboratory according to laboratory procedures. Genomic analysis will be performed using a validated assay method under the supervision of the Sponsor. Only samples which are within the window of sample stability will be analyzed.

8.1.8 QUALITY OF LIFE ASSESSMENTS

8.1.8.1 SHORT FORM 36 HEALTH SURVEY (SF-36)

The SF-36 is a generic questionnaire measuring general health status (QoL) in the last 4 weeks before completing the questionnaire. The SF-36 is a 36-item questionnaire that measures 8 multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items).

For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardized summary scores can also be calculated from the SF-36; the physical component summary and the mental health component summary. The time for completion is 5 to 10 minutes.

The SF-36 will be completed as indicated in the SoA (see Section 1.3) and is located on the clinical tablet.

A sample SF-36 is provided in Appendix F.

8.1.8.2 EUROPEAN QOL SCALE (EQ-5D)

The EQ-5D is a standardized health-related QoL questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal and inter-disease comparisons. The EQ-5D is designed for self-completion by subjects and takes only a few minutes to complete.

The EQ-5D was used to study the impact on QoL for filgrastim administration in CRS patients, the scores improved though they were not statistically significant (*Van Agthoven et al., 2001*).

The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problem, some problems, severe problems. The EQ VAS records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

The EQ-5D will be completed as indicated in the SoA (see Section 1.3) and is located on the clinical tablet.

A sample EQ-5D is provided in Appendix G.

8.1.8.3 7-ITEM ASTHMA CONTROL QUESTIONNAIRE (ACQ-7)

The ACQ-7 will be used in this study to assess the asthma symptoms (nocturnal waking, symptom on waking, activity limitation, and shortness of breath, wheezing, and short acting β agonist [SABA] usage) and FEV_1 measurement in subjects with active asthma disease. Subject will be asked to recall their

experiences during the previous week by responding to 5 symptom related questions and 1 question related to bronchodilator use. Questions will be scored from 0 (totally controlled) to 6 (severely uncontrolled). The questionnaire will be administered only in subjects with active asthma disease. The subject should complete the ACQ 7 at the time points indicated in the SoA (see Section 1.3) and is located on the clinical tablet.

A sample ACQ-7 is provided in Appendix H.

8.1.8.4 EXCLUDED MEDICATIONS PRIOR TO LUNG FUNCTION ASSESSMENTS

For subjects taking asthma medications, asthma medications should be withheld prior to lung function tests on study visit days:

- Short acting bronchodilators (eg, albuterol [salbutamol] or ipratropium) should be withheld for at least 6 hours before spirometry.
- Twice daily long-acting bronchodilator (LABA or long-acting muscarinic antagonist [LAMA] containing therapies) should be withheld for 12 hours and once daily long-acting bronchodilator (LABA or LAMA containing therapies) for > 12 hours before spirometry.
- Leukotriene receptor antagonists (LTRA) should be restricted for > 12 hours.
- Twice daily theophylline should be withheld for at least 12 hours and once daily theophylline for > 12 hours before spirometry.
- If a subject has taken rescue SABA within 4 hours of the planned spirometry study center visit, they should either:
  - Remain at the study center until the 4-hour withholding time has been reached OR
  - Return on the following day (or within study window) for lung function assessments.

8.1.8.5 NASAL POLYP RELATED RESOURCE USE QUESTIONNAIRE

The Nasal Polyp Related Resource Use Questionnaire is a questionnaire of health care resource utilization for nasal polyposis (eg, specialist visits, emergency care visits, sick leaves, days off) will be completed as indicated in the SoA (see Section 1.3) and is located on the clinical tablet.

A sample Nasal Polyp Related Resource Use Questionnaire is provided in Appendix I.

8.1.8.6 SPIROMETRY (FEV_1 MEASUREMENT)

Spirometry will be performed on all subjects at the time points indicated in the SoA (see Section 1.3) and according to the ATS/ERS guidelines. Sites should perform spirometry using the spirometer provided by ERT. The spirometer should be calibrated per ATS/ERS guidelines prior to the start of the lung function

assessment on each study center visit day. The spirometer should be set to use the Global Lung Function Initiative reference equations, results will be over read by ERT.

Pre-bronchodilator spirometry will be performed after appropriate bronchodilator withholding period in the morning. Patients with active asthma should withhold their usual asthma therapy prior to lung function tests on the study visit days spirometry is performed. See Section 8.1.8.4 for prohibited medications prior to lung function assessments.

Subjects should have spirometry performed at approximately the same time on each study center visit day. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted; however, the same position should be used by the patient for each forced expiratory maneuver from Screening through EOS visit. Three acceptable maneuvers should be obtained for each test. Additional details are provided in the lung function testing manual provided by the vendor.

8.1.8.7 VISUAL ANALOGUE SCALE

The VAS for rhinosinusitis is used to evaluate the total severity and is validated in adult CRS (*Fokkens et al., 2012*).

The subject is asked to indicate on a VAS the answer to the question: “How troublesome are your symptoms of rhinosinusitis?“ The VAS ranks from 0 (Not troublesome) to 10 (Worst thinkable troublesome).

The disease can be divided into mild, moderate, and severe based on total severity VAS score (0 to 10 cm):

MILD = VAS 0-3

MODERATE = VAS >3-7

SEVERE = VAS >7-10

The VAS will be used as indicated in the SoA (see Section 1.3).

The VAS scale will be collected weekly in the eDiary. On Day 1, the eDiary must be provided to the subject prior to dosing and the subject must complete the VAS scale before receiving study drug.

A sample VAS is provided in Appendix J.

8.2 SAFETY AND OTHER ASSESSMENTS

Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

8.2.1 CLINICAL LABORATORY DATA

Table 1 lists the clinical laboratory tests to be assessed in this study. As outlined in the SoA (Section 1.3), non-fasting samples for serum chemistry, hematology, pregnancy test, serum antibodies and urinalysis will be collected at designated study timepoints. Blood and urine specimens will be collected using applicable safety precautions and processed according to clinical laboratory instructions.

Table 1. Clinical Laboratory Tests

Laboratory Assessments	**Parameters**	
Hematology	Hemoglobin Hematocrit Mean cell hemoglobin Mean cell volume Mean cell hemoglobin concentration Platelet count Red blood cell count	White blood cell count with differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	ALT Albumin Alkaline phosphatase AST Bicarbonate Bilirubin (total) Bilirubin (direct-only if total is elevated) Calcium Chloride Uric acid Lactate dehydrogenase Troponin-I Creatine kinase	Creatinine Gamma glutamyl transferase Glucose Potassium Phosphate (inorganic) Protein (total) Sodium Blood urea nitrogen (urea) C-reactive protein Triglycerides Total cholesterol (fractions)
Follicle stimulating hormone	As needed in women of non-childbearing potential only (postmenopausal woman aged over 45 years with at least 1 year of amenorrhea)	
Serum pregnancy	Human chorionic gonadotropin pregnancy test (as needed for WOCBP)	
Urine pregnancy	Urine pregnancy dipstick (prior to study treatment administration)	

Laboratory Assessments	Parameters	
Urinalysis (dipstick test)	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrites	pH Protein Specific gravity Urobilinogen
Immunoglobulin	Immunoglobulin E	
Drugs of Abuse (Urine drug screen)	Methamphetamine Cocaine Marijuana MDMA Methadone Opiate Ethanol	Benzodiazepines Barbiturates Phencyclidine Amphetamine Oxycodone TCA
Viral serology	Hepatitis B surface antigen Hepatitis B and C antibodies HIV antibodies (HIV 1 and 2)	
Tuberculosis B (TB) test	Subjects with an indeterminate QuantiFERON® TB Gold result at Screening will be allowed one retest. purified protein derivative (PPD) test is permitted as repeat test in subjects who have never had a bacille Calmette-Guerin (BCG) vaccination.	

The results of each local test must be entered into the eCRF.

Abbreviations: ADA = anti-drug antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form, HIV = Human Immunodeficiency Virus, MDMA = Methylenedioxymethamphetamine, PK = Pharmacokinetics and TCA=Tricyclic anti-depressants.

NOTES: Please see SoA (see Section 1.3) for laboratory tests time points. PK and ADA samples will be collected as detailed in the SoA (see Section 1.3). Samples should be obtained prior to administering study drug if an administration coincides with the visit and before any hematology, or chemistry, samples to be drawn at that visit. The date and exact time of sample collection must be recorded.

- It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. Likewise, if laboratory tests are taken at follow-up visits, the Investigator must ascertain if this is an abnormal and clinically significant change posttreatment for that individual subject. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

- The Investigator or qualified designee must sign and date all written laboratory results (chemistry, hematology plus pregnancy test, and urinalysis) and note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out-of-range laboratory value. If a laboratory value is

determined to be a CS result for that subject, this may be considered an AE. Record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- A central laboratory will be used to perform all laboratory tests except urine pregnancy dipstick which will be assessed by the site staff. However, local laboratory tests will be allowed if the central laboratory results will not be available immediately because the investigator needs to make an immediate decision for any safety concerns based on laboratory results.

- All laboratory tests with values considered CS abnormal during participation in the study including the subject's last EOS visit should be repeated until the values return to normal or baseline or are no longer considered CS or judged medically stabilized by the investigator or Medical Monitor. Clinically significant abnormal laboratory results should be reported as an AE or SAE if applicable.

- If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined above, must be conducted in accordance with the Laboratory Manual and the SoA (see Section 1.3).

- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered CS by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF and the laboratory reports must be filed with the source documents.

8.2.2 PREGNANCY TESTING

All WOCBP will have a serum pregnancy test (SPT) at Screening and urine pregnancy test (UPT) at all designated post-screening timepoints as indicated in the SoA (Section 1.3). If UPT is positive, a SPT will be performed to confirm. If any result is positive prior to IP administration, the subject will not be allowed to participate. Follicle stimulating hormone may be used to confirm menopausal status in female subjects as needed. Refer to Appendix B for further information.

8.2.3 PHYSICAL EXAMINATION

A complete physical examination will include examination of the following parameters and body systems: skin, neck (including thyroid), head, eyes, ears, nose, throat, heart, lungs, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

At Screening, a complete physical examination will be performed. At baseline and posttreatment visits, the physical examination may be abbreviated, as deemed medically appropriate at the discretion of the Investigator.

Significant physical examination findings which meet the definition of an adverse event will be recorded on the AE page posttreatment; significant findings that are present prior to IP administration are included on the medical history page.

8.2.4 VITAL SIGNS

Vital signs captured include body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic BPs. Vitals should be collected before blood sampling and before injection of study drug at each visit where administered (see Section 1.3). Blood pressure is collected after 15 minutes of rest in a seated position.

8.2.5 12-LEAD ECG

A single, standard, supine 12-lead ECG will be obtained after a subject has rested quietly for at least 10 minutes, using equipment provided from the central reader. The ECG is to be repeated up to 2 times if the result is abnormal, as clinically appropriate. ECGs must be collected on the ECG machine provided by ERT. ECG data will be submitted and reviewed by the central reader. The ECG will also be reviewed by the investigator or an authorized representative who is experienced in the evaluation of ECGs and assessed for clinical significance.

Instructions and guidelines for collection (eg, equipment), transmission, and archiving of ECG data will be provided in the ECG Manual. A 12-lead ECG will be obtained using a validated ECG machine that automatically calculates the HR and measures pulse rate, QRS, QT, and QTc intervals.

8.2.6 INJECTION SITE EVALUATION

Subjects must remain onsite for 2 hours postdose for observation at the Day 1 (Week 0) visit. Injection sites will be evaluated to determine if there are any injection site reactions to the IP. Any injection-related pain, redness, bruising or swelling, etc., will be reported as an AE.

8.3 PHARMACOKINETICS

Whole blood samples will be collected for measurement of serum concentrations of etokimab at time points as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by BARC central laboratory and analyzed by Q2 Solutions. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Samples will be used to evaluate the PK of etokimab. Each serum sample will be divided into 2 aliquots (1 for a primary PK sample and 1 for a back-up PK sample). Samples collected for analyses of etokimab serum concentration may also be used to correlate exposure to safety or efficacy aspects related to concerns arising during or after the study.

Measurement of concentrations of etokimab will be performed using a validated assay method. Only samples which are within the window of sample stability will be analyzed. The time points for PK sample collection is given in Appendix D.

While PK and immunogenicity samples must be collected from subjects assigned to the placebo arm to maintain the blinding of treatment assignment, PK and immunogenicity assay results for these subjects are not needed for the safe conduct or proper interpretation of this trial and the samples will therefore not be analyzed. Personnel responsible for performing PK assays will be unblinded to subjects' treatment assignments in order to identify appropriate PK and immunogenicity samples to be analyzed. Samples from subjects assigned to the placebo arm may be analyzed upon request (ie, to evaluate a possible error in dosing).

Genetic analyses will not be performed on these samples unless the separate pharmacogenomics consent has been signed. Subject confidentiality will be maintained. Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and study center study files, but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

If a subject refuses blood collection for PK analysis, this will not be considered a protocol deviation as the PK analysis is a secondary objective.

8.4 BIOMARKERS

No specific or exploratory biomarkers will be collected or analyzed in this study.

8.5 IMMUNOGENICITY

Antibodies to etokimab will be evaluated in serum samples collected from all etokimab-dosed subjects according to the SoA (See Section 1.3). Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples

will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for immunogenicity testing and a back-up).

Serum samples will be tested in a multi-tiered approach. A validated screening assay for antibodies binding to etokimab will be initially used to assess serum samples. Samples that are determined putative positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that antibodies are specific to etokimab. Samples that are identified as positive in the confirmatory assay will be further characterized in a validated titer assay and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment.

The detection and characterization of antibodies to etokimab will be performed using a validated assay method by or under the supervision of the sponsor. Only samples which are within the window of sample stability will be analyzed. The time points for ADA sample collection is given in Appendix C.

Samples that are confirmed positive for antibodies binding to etokimab with a titer greater than the minimum required dilution of the validated assay may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment using a validated cell based neutralizing antibody assay method.

8.6 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.6.1 DEFINITION OF ADVERSE EVENTS

For this protocol, an AE is any untoward medical occurrence (eg, sign, symptom, disease, syndrome, intercurrent illness, CS abnormal laboratory finding, injury, or accident) that emerges or worsens following administration of the study drug and until the EOS participation. The untoward medical occurrence may not necessarily have a causal relationship to the administration of the IP. An AE can therefore be any unfavorable and/or unintended sign (including a CS abnormal laboratory result), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A treatment-emergent AE is one that occurs after any exposure to treatment.

A pre-existing condition is one that is present prior to the start of the study and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

Any CS change in the study safety evaluations, (eg, vital signs, physical/neurological examinations, etc.) post injection must be reported as an AE.

For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a CS result for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed; the Investigator may repeat

the laboratory test or request additional tests to verify the results of the original laboratory test. If a laboratory value is determined to be a CS result for a subject, this may be considered an AE.

8.6.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening (ie, the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe.)
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization (ie, a prolonged hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (ie, an adverse outcome in a child or fetus of a subject exposed to the molecule or IP before conception or during pregnancy)
- Does not meet any of the above serious criteria but based upon appropriate medical judgment may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (ie, is a significant or important medical event)

8.6.3 CLASSIFICATION OF AN ADVERSE EVENT

8.6.3.1 SEVERITY OF EVENT

The Investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized as mild, moderate, or severe according to the following definitions:

- **Mild:** Event may be noticeable to subject; does not influence daily activities; usually does not require intervention.
- **Moderate:** Event may be of sufficient severity to make a subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.
- **Severe:** Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed.

8.6.3.2 RELATIONSHIP TO STUDY INTERVENTION

Relationship of an AE to IP will be assessed as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of IP when the event responds to withdrawal of IP and recurs with re-administration of IP.

- **Related:** There is a clinically plausible time sequence between the onset of the AE and the administration of IP; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures.

- **Possibly Related:** There may or may not be a clinically plausible time sequence between the onset of the AE and the administration of IP and a cause cannot be ruled out.

- **Unrelated:** There is not a temporal or causal relationship to IP administration.

8.6.3.3 EXPECTEDNESS

The PI/designee will be responsible for determining whether an AE is expected or unexpected. An unexpected AE is one not identified in nature, severity, or frequency in the current protocol or IB.

8.6.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

SAEs that are identified on the last scheduled contact must be recorded on the AE eCRF page and reported to the Sponsor or the authorized representative according to the reporting procedures outlined in Section 8.6.6. This may include unresolved previously reported SAEs, or new SAEs. The Investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. The Investigator should continue to report any significant follow-up information to the Sponsor or the authorized representative, and the IRB, up to the point the event has been resolved. Resolution means the subject has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled contact and are determined by the Investigator to be reasonably associated with the administration of IP should be reported to the Sponsor or the authorized representative, and the IRB, as required.

8.6.5 ADVERSE EVENT REPORTING

The Investigator will assess subjects at each study visit and posttreatment per protocol for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and eCRFs.

Adverse Events will be recorded beginning from the time of consent. Adverse Events that occur prior to dosing will also be noted in the medical history.

8.6.6 SERIOUS ADVERSE EVENT REPORTING

The Investigator will report any SAE to th [redacted] Pharmacovigilance within 24 hours of being made aware of it, whether or not considered study intervention related, including those listed

in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (eg, all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis). In that case, the Investigator must report the event to the Sponsor in the shortest possible time.

All SAEs will be followed until satisfactory resolution or until the study center Investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the local or centralized IRB and study Sponsor and should be provided as soon as possible.

The study Sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information and in compliance with the 15 day requirement. In addition, the Sponsor must notify FDA and all participating Investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

8.6.7 REPORTING EVENTS TO PARTICIPANTS

The Sponsor will disclose clinical trial data to individuals, to Investigators at sites, and publicly as aggregate summaries, in accordance with applicable regulations and requirements.

8.6.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.6.9 REPORTING OF PREGNANCY

During the trial, all WOCBP should be instructed to contact the Investigator immediately (within 24 hours) if they suspect they might be pregnant (eg, missed or late menstrual cycle). The Investigator must immediately notify [redacted]Pharmacovigilance of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and send the form to the authorized representative. The study center will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Subjects who become pregnant during the study will be discontinued.

In the case of male subject’s female partner becoming pregnant while the male subject is in this study, the Investigator should attempt to collect pregnancy information on the male subject’s female partner. This applies only to male subjects who receive study treatment.

The Investigator will record pregnancy information on the appropriate pregnancy form and submit it to the sponsor within 24 hours of learning of the partner’s pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following

the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.7 UNANTICIPATED PROBLEMS

8.7.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.7.2 UNANTICIPATED PROBLEM REPORTING

The Investigator will report unanticipated problems (UPs) to the reviewing IRB and to the Data Coordinating Center (DCC)/lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study Sponsor within 24 hours of the Investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to the DCC/study Sponsor within <7 days of the Investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), and the supporting agency head (or designee) within 14 days of the IRB's receipt of the report of the problem from the Investigator.

8.7.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The Sponsor will disclose clinical trial data to individuals, to Investigators at sites, and publicly as aggregate summaries, in accordance with applicable regulations and requirements.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the efficacy of etokimab compared to placebo in the treatment of subjects with CRSwNP following a 16-week treatment period (change from baseline using co-primary endpoints). The hypotheses for the co-primary efficacy endpoints are delineated below.

Co-Primary Efficacy Endpoints:

Statistical hypotheses associated with the co-primary efficacy endpoints are as follows:

- Treatment of adults diagnosed with CRSwNP using etokimab will result in a significantly greater reduction of Week 16 NPS from baseline when compared to placebo, and

- Treatment of adults diagnosed with CRSwNP using etokimab will result in a significantly greater reduction of Week 16 SNOT-22 score from baseline when compared to placebo

9.2 SAMPLE SIZE DETERMINATION

Sample size estimates were calculated based on the following assumptions:

- Overall alpha=0.05
- Co-primary endpoints
- Hierarchical testing of the 2 active treatment arms versus placebo
- At least 85% power to detect a clinically meaningful difference between etokimab and placebo

Based on data from similar trials conducted in adult subjects with CRSwNP, a difference in NPS of 1.3 between the etokimab change from Baseline to Week 16 and the placebo group change from Baseline to Week 16 will be clinically meaningful (*Bachert et al. 2016*). Assuming a standard deviation (SD) of 1.5, and a significance level of 5%, a sample size of n=27 for each treatment arm will provide approximately 87% power to detect the stipulated difference. In order to account for the dilution of treatment effect due to 18% dropouts and missing data, approximately 33 subjects are planned to be randomized equally to each of the 3 treatment arms.

The second co-primary endpoint is SNOT-22 total score. In a trial of adults with CRSwNP, the difference in mean change from Baseline to Week 16 between active and placebo was 18.1. Assuming a common standard deviation of 19.2, and 2-sided significance level of 5%, the sample size of 27 subjects provides 92% power to detect the stipulated treatment difference. Hence, adjusting for 18% dropouts and missing data, n=33 subjects will provide >85% desired power to detect a clinically meaningful difference in this endpoint between each active arm and placebo.

9.3 ANALYSIS SETS

The analysis sets for evaluating the efficacy, safety, and pharmacokinetics of etokimab are defined in Table 2.

Table 2. Analysis Sets

Analysis Set	Description
Safety Analysis Set	The safety analysis set will include all randomized subjects who receive 1 dose of etokimab or placebo. The safety analysis set will be used for all safety analyses. Subjects will be analyzed as treated.
Full Analysis Set	The full analysis set (FAS) will include all randomized subjects who receive 1 dose of etokimab or placebo and have baseline and at least 1 post baseline NPS and/or SNOT-22 scores up to Week 16. The full analysis set will be used for all efficacy analyses. Subjects will be analyzed as randomized.
PP Analysis Set	The PP (Per Protocol) analysis set will include all subjects in the FAS analysis set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoints.
PK Analysis Set	The PK analysis set will include all subjects in the safety analysis set who have at least one quantifiable postdose PK sample available and who do not have events or protocol deviations or events with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

Abbreviations: FAS = Full analysis set, PP = Per protocol, PK = Pharmacokinetics.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The final statistical analysis will be performed after all reportable data have been collected, queries resolved, and the database locked. The Statistical Analysis Plan (SAP) will be developed and finalized before the database lock and will provide full details of all statistical analyses, including procedures for accounting for missing, unused, and spurious data. This section summarizes the planned statistical analyses of the primary and secondary endpoints.

The statistical analyses will be performed using statistical analysis system (SAS®) version 9.4 or higher if available. All details regarding the statistical analyses and the preparation of tables, listings and figures will be described in the SAP.

In general, continuous variables will be summarized with descriptive statistics including n, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by the number and percentage of subjects in the relevant analysis set and treatment group falling into each category.

Unless otherwise specified, “baseline” is defined as the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). For numerical variables, change from baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

Unless otherwise specified, all formal statistical tests will be 2-sided at the 5% significance level. Point estimates will be accompanied with 2-sided 95% confidence intervals (CIs), where applicable. In the case of normality assumption violations, appropriate nonparametric methods will be used for analysis.

All data will be presented in by subject and treatment listings.

9.4.2 EFFICACY ANALYSES

A summary of the efficacy endpoints (co-primary, secondary, and exploratory) and the statistical methods that will be used to analyze these endpoints is provided in Table 3. The co-primary efficacy analyses will be performed on the FAS. Additionally, the co-primary efficacy analyses will be repeated on the PP Analysis set.

Table 3. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Co-Primary Efficacy:	
Change from baseline to Week 16 in bilateral endoscopic NPS	General linear mixed effects model with repeated measures (MMRM) including the change from baseline in NPS as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline NPS score as covariate; and subject as random effect.
Change from baseline to Week 16 in SNOT-22 scores	MMRM as above for NPS will be applied for SNOT-22 score.
Secondary Efficacy:	
Time to first response (≥1 point reduction in NPS)	Log rank test to compare the time to first response for the treatments
Responder analysis*:* response defined as a reduction of ≥1point from baseline to Week 16 in NPS	Logistic regression modeling the response as dependent variable, treatment, baseline NPS, and asthma comorbidity as covariates
Responder analysis response defined as a reduction of ≥12 points from baseline to Week 16 in SNOT-22	Logistic regression modeling the response as dependent variable, treatment, baseline SNOT-22 score, and asthma comorbidity as covariates
Change from baseline to Week 16 in UPSIT	MMRM proposed for NPS will be applied for UPSIT.

Endpoint	Statistical Analysis Methods
Exploratory Efficacy	
Change from baseline to Week 16 in sinus opacification as assessed by CT scan using Lund-Mackay score	Analysis of covariance (ANCOVA) modeling the change from baseline in Lund-MacKay score at Week 16 as dependent variable; baseline Lund-MacKay score as covariate; and treatment as a factor
Change from baseline to Week 16 in AM NPIF	MMRM, including the change from baseline in AM NPIF as the dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline AM NPIF score as covariate; and subject as a random effect
Change from baseline to Week 16 in PM NPIF	MMRM, including the change from baseline in PM NPIF as the dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline PM NPIF score as covariate; and subject as a random effect
Change from baseline to Week 16 in bilateral endoscopic NPS in subjects with comorbid asthma	MMRM including the change from baseline in NPS as dependent variable; treatment group, time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors; baseline NPS score as covariate; and subject as random effect
Change from baseline to Week 16 in SNOT-22 in subjects with comorbid asthma	MMRM as above for NPS will be applied for SNOT-22 score
Change from baseline to Week 16 in the percent of 3-dimentional volumetric maxillary sinus occupied by disease (%VMSOD) as assessed by CT scan	Analysis of covariance (ANCOVA) modeling the change from baseline in %VMSOD score at Week 16 as dependent variable; baseline %VMSOD score as covariate; and treatment as a factor
Change from baseline to Week 16 in SF-36 physical component summary (PCS)	MMRM including the change from baseline in SF-36 PCS score as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline SF-36 PCS score as covariate; and subject as a random effect
Change from baseline to Week 16 in SF-36 mental component summary (MCS)	MMRM as above for SF-36 PCS will be applied for SF-36 MCS

Endpoint	Statistical Analysis Methods
Change from baseline to Week 16 in EQ-5D index score	MMRM including the change from baseline in EQ-5D index score as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline EQ-5D index score as covariate; and subject as a random effect
Change from baseline to Month 4 in VAS	MMRM including the change from baseline in VAS score as dependent variable; treatment group, stratification factor, time (Months 1, 2, 3, and 4), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline VAS score as covariate; and subject as a random effect
Number of nocturnal awakenings (in subgroup with comorbid asthma)	Cochran Mantel-Hanszel statistics testing the row mean scores differ between treatment groups at each visit
Change from baseline to Week 16 in FEV_1 (overall and in subgroup with asthma)	MMRM including the change from baseline in FEV_1 score as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline FEV_1 score as covariate; and subject as a random effect
Change from baseline to Week 16 in % predicted FEV_1 (overall and in subgroup with asthma)	MMRM including the change from baseline in %predicted FEV_1 score as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline %predicted FEV_1 score as covariate; and subject as a random effect
Change from baseline to Week 16 in ACQ-7 total score in subjects with comorbid asthma	MMRM including the change from baseline in ACQ-7 score (mean of the responses to all 7 questions) as dependent variable; treatment group, time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors; baseline ACQ-7 score as covariate; and subject as a random effect

Endpoint	Statistical Analysis Methods
Change from baseline to Week 16 in blood eosinophil count	MMRM modeling the change from baseline in blood eosinophil count at Week 16 as dependent variable; treatment group, stratification factor, time (Weeks 4, 8, 12, and 16), treatment by stratification factor, and treatment by time interaction as fixed effect factors; baseline blood eosinophil count as covariate; and subject as a random effect
Time to study treatment discontinuation	Log rank test to compare the time to study treatment discontinuation
Incidence of treatment discontinuation due to need for OCS or nasal polyp surgery	Fisher's exact test comparing the proportion of subjects with treatment discontinuation due to need for OCS or nasal polyp surgery
Nasal Polyp Resource Questionnaire at each visit	Descriptive statistics (number, percentage) to be provided per questionnaire item per visit

Abbreviations: ANCOVA = analysis of covariance, CT = computed tomography, EOT = end of treatment, EQ-5D = EuroQoL-5D Scale, MMRM = mixed effects model with repeated measures, MPS = mental component summary, NPIF = nasal peak inspiratory flow, NPS = Nasal Polyp Score, PCS = physical component summary, SF-36 = Short Form 36 Health Survey, SNOT-22 = Sino-Nasal Outcome Test, UPSIT = University of Pennsylvania Smell Identification Test, VMSOD = volumetric maxillary sinus occupied by disease

Statistical significance for the co-primary efficacy endpoints will be declared if both p-values for the tests of the individual hypotheses, as described below, are < 0.05.

9.4.2.1.1 FIRST CO-PRIMARY ENDPOINT

The first co-primary endpoint is the change from Baseline to Week 16 in bilateral endoscopic NPS while on treatment.

Baseline endoscopic NPS is the sum of the left and right nasal polyposis score at the randomization visit. The NPS is also measured every 4 weeks during treatment and at end of treatment (Week 16). A general linear MMRM using change from baseline in NPS scores at Weeks 4, 8, 12, and 16 as response, stratification factor, treatment group as fixed effect (3 levels), treatment by stratification factor, and treatment by time interaction as fixed effects, Baseline (Day 1) NPS score as fixed continuous covariate, and subject as a random effect, will be used to obtain least squares means at EOT, to compare the etokimab treatment arms with the placebo arm.

No imputation of data for missing data due to treatment discontinuation will be implemented in the primary analysis. Comparison of the treatment arms will be based on the Week 16 least squares means of the treatment arms. An unstructured covariance matrix will be assumed and estimated in order to obtain associated standard errors for least squares means and to carry out the treatment comparisons. In case of convergence problems for the maximum likelihood estimates, other covariance structures with fewer parameters may be sought from the range of options provided in SAS PROCEDURE MIXED.

Comparison of each treatment arm with placebo will be based on the Week 16 least squares means obtained from the MMRM, where missing data due to treatment discontinuation are regarded as missing at random. Testing will be conducted in a hierarchical manner such that the comparison of the etokimab every 4 weeks treatment arm versus placebo will be conducted first. If the results of the comparison of the etokimab every 4 weeks treatment arm versus placebo are statistically significant, the etokimab every 8 weeks treatment arm will be compared to placebo. The p-value for the comparison will be obtained and compared to the significance level of 5%. An associated 2-sided 95% confidence interval will be obtained for the active minus placebo change from baseline to week 16 in the NPS for each treatment arm tested. No further adjustment will be made for testing each dosing regimen with placebo.

In order to assess the impact of missing data due to treatment discontinuation, a sensitivity analysis may be performed where their data after dropout will be imputed using multiple imputation and the statistical analysis using MMRM will be repeated. Another sensitivity analysis may be performed where observed values of the NPS score obtained during study but after treatment discontinuation, if available, will be used. The MMRM model will be utilized where the treatment discontinuations are regarded as not missing at random (NMAR). Full details will be specified in the SAP.

9.4.2.1.2 SECOND CO-PRIMARY ENDPOINT

The second co-primary endpoint is the change from Baseline to Week 16 in SNOT-22 scores.

An MMRM as described above for NPS, using the Baseline (Day 1) SNOT-22 score as fixed covariate, will be utilized for the SNOT-22.

Baseline endoscopic NPS is the sum of the left and right nasal polyposis score at the randomization visit.

Comparison of each treatment arm with placebo will be based on the Week 16 least squares means obtained from the MMRM. The p-value for the comparison will be obtained and compared to the significance level of 5%. An associated 2-sided 95% CI will be obtained for the active minus placebo change from baseline to Week 16 in the SNOT-22. No further adjustment will be made for testing each dosing regimen with placebo.

In order to assess the impact of missing data due to treatment discontinuation, a sensitivity analysis may be performed where their data after treatment discontinuation will be imputed using multiple imputation and the statistical analysis using MMRM will be repeated. Another sensitivity analysis may be performed where observed values of the SNOT-22 score obtained during study but after treatment discontinuation, if available, will be used. The MMRM model will be utilized where the treatment discontinuations are regarded as NMAR. Full details will be specified in the SAP.

9.4.2.2 ANALYSIS OF THE SECONDARY AND EXPLORATORY ENDPOINT(S)

Analysis of secondary efficacy endpoints will be performed in a hierarchical order as listed in Section 3 to adjust for statistical multiplicity. More details for multiplicity adjustment will be described in SAP.

For the secondary PK endpoints, primary PK parameters of CL/F and volume of distribution will be estimated by population PK modeling from ANB020 serum concentrations after SC administrations. Secondary PK parameters of AUC_{tau}, C_{max}, t_{max}, for the first dose and AUC_{tau}, C_{max}, t_{max} and $T_{1/2}$ for the last dose will also be calculated for ANB020 after SC administrations, where possible, using a Bayesian post-hoc estimation approach based on the aforementioned population PK model. Other parameters may be evaluated, if needed. The PK parameters will be listed and summarized using appropriate descriptive statistics. Pharmacokinetic concentration data collected from the study may be included in a population PK based (meta) analysis, using non-linear mixed effects modeling. The data from this study may be combined with data collected from other studies for population PK model development. A covariate screen of subject specific factors (eg, demographic and clinical characteristics) will be included in the analyses. Any population PK analysis plan will be described in detail in a pharmacometric analysis plan.

All secondary and exploratory efficacy analyses will be performed on the FAS. Table 3 includes a summary of the statistical methods to be used in analyzing efficacy endpoints (co-primary, secondary, and exploratory). Full details of statistical analysis for all secondary and exploratory endpoints will be provided in the SAP.

9.4.2.3 HANDLING OF DROPOUTS AND MISSING DATA

Every effort should be made to minimize dropouts and missing assessment data. Subjects should be reminded of the importance of providing assessments as per protocol, and study personnel should be vigilant in ensuring assessments are completed as scheduled.

Nonetheless, as subjects may elect to be withdrawn from study treatments or evaluations without prejudice, it is inevitable that there will be missing data. Subjects who elect to discontinue their randomized treatment but consent to continue in the study may provide on-study but off-treatment assessments which will aid in providing sensitivity analyses for the co-primary endpoints.

The handling of missing data in the statistical analyses of the efficacy endpoints will be fully detailed in the SAP.

No imputation of values for safety endpoints will be made. The SAP will provide methods for handling partial or completely missing assessment dates or missing adverse event severity.

9.4.3 SAFETY ANALYSES

9.4.3.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A TEAE is defined as:

- A new event that occurs during or after first dose of study treatment or,
- Any event present at baseline that worsens in either intensity or frequency after first dose of study treatment.

TEAEs and SAEs will be summarized.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and percentage will be tabulated by preferred term (PT) and system organ class (SOC). An event that occurred 1 or more times on treatment period will contribute 1 observation to the numerator and denominator comprise all safety subjects exposed to etokimab. If the intensity or seriousness of the TEAE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences. The TEAEs, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to withdrawal of subject will be tabulated for each treatment group. Summaries will also be presented by relatedness to the study drug and the severity of the TEAE.

Listings of AEs, TEAEs, TEAEs leading to death, SAEs, and TEAEs that led to discontinuation from the study or of the study drug will be presented.

Injection site reaction will be reported separately by treatment.

9.4.3.2 DEATHS

Subject deaths will be presented in a by-subject listing.

9.4.3.3 PHYSICAL EXAMINATIONS, 12-LEAD ECG, VITAL SIGNS, AND CLINICAL SAFETY LABORATORY TESTS (HEMATOLOGY, BIOCHEMISTRY, AND URINALYSIS)

Summaries and listings of data for both limited and complete physical examination findings, vital signs, hematology, biochemistry, and urinalysis laboratory tests will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from baseline.

For hematology and biochemistry tests, listings of subject data will also flag any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and clinical laboratory data will be reported in System International units.

Descriptive statistics will be used to present the safety outcomes including, physical examination results, weight, BMI, 12-lead ECG, vital signs measurements, and clinical laboratory test results.

Change from baseline will also be summarized for vital signs measurements, and clinical laboratory test results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentages. Clinically significant abnormalities will be presented in by subject listings.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

9.4.4.1 SUBJECT DISPOSITION

A tabular presentation of the subject disposition will be provided. It will include the number of subjects screened, randomized, treated, completed as well as the number of study discontinuations, with reasons for discontinuation, and major protocol deviations or violations.

A listing will be presented to describe date of Screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations/violations will be identified and discussed with the Investigator and Sponsor in dry run to categorize as major or minor and the same will be reported.

9.4.4.2 SUBJECT CHARACTERISTICS AND MEDICAL HISTORY

Subject characteristics obtained at Screening will be summarized for all subjects taking etokimab. Subject characteristics may include, but are not limited to age, gender, height, weight, and BMI.

Summaries will include descriptive statistics for continuous variables (sample size [n], mean, SD, median, minimum, and maximum) and for categorical variables (sample size, frequency, and percent).

Medical history will be coded using the MedDRA dictionary latest version and listed for all subjects.

9.4.4.3 CONCOMITANT MEDICATIONS

All medications will be coded using the World Health Organization Drug Dictionary. Each medication will be classified as prior medication if it is stopped prior to the first dose of study drug, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study drug. Prior, concomitant, and rescue medications will be summarized by Anatomic Therapeutic Chemical (ATC) level 2 categories, and preferred name.

9.4.5 PLANNED INTERIM ANALYSES

An interim analysis of co-primary data is planned when approximately 84 randomized subjects have completed Week 8 of the study. The rationale for this analysis is to assist in making decisions for the Phase 3 program. No adjustments to the current protocol are planned as a result of the interim analysis. Therefore, overall alpha is expected to be maintained at 0.05, 2-sided, for the co-primary efficacy endpoints.

Full details on the interim analysis process, procedures for maintaining confidentiality of the interim analysis results will be described in the SAP and in the DSMB analysis plan, as appropriate.

9.4.6 SUBGROUP ANALYSES

Subgroup analysis are planned for subjects with asthma comorbidity as indicated in Section 9.4.2. Any other subgroup analyses will be detailed in the SAP.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All individual subject data will be listed by treatment group in the appendices.

9.4.8 IMMUNOGENICITY ANALYSES

Observed values for ADA levels/status will be listed by subject and summarized with descriptive statistics based on the safety analysis set. If data permits, correlation will be analyzed between ADA levels and safety and efficacy endpoints.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the subject's agreeing to participate in the study and continues throughout the subject's study participation. Written informed consent will be obtained from all subjects before any study-related procedures (including any pre-treatment screening procedures) are performed. The Investigator may discuss the study and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The Investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this study has been given a full explanation of the procedures and expectations for study participation.

When applicable, the study center-specific informed consent must be forwarded to the Sponsor for approval prior to submission to an IRB that is registered with appropriate local or federal agencies as required. Each subject will sign the consent form that has been approved by the same IRB that was responsible for protocol approval. Each informed consent document must adhere to the ethical

principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by the International Council on Harmonisation (ICH) GCP guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that the Sponsor, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study-related purposes.

Once the appropriate essential information has been provided to the subject and fully explained by the Investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the study, the IRB approved consent document shall be signed and dated by both the subject and the person obtaining consent (Investigator or designee), and by any other parties required by the IRB or other regulatory authorities. The subject will be given a copy of the signed informed consent document with the original kept on file by the Investigator. All of the above activities must be completed before any study-related procedures are conducted (including any screening study procedures).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, Investigator, the IND Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study subjects, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study drug may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study center will permit access to such records.

The study subject's contact information will be securely stored at each clinical study center for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study sites and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study IP, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor. Subjects will only be identified by unique subject numbers on eCRFs.

Every subject will be given a copy of each version of the form that he/she signs before and during the study. Each ICF may also include authorization allowing the institution, Investigator, and Sponsor to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 Health Information Portability and Accountability Act (HIPAA).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Blood and serum specimen storage outside the study required assessments is optional and requires subjects to sign a separate ICF. Refusal to participate in this optional DNA collection and specimen storage does not affect a subject's ability to be enrolled in the study. A subject may choose to participate in this DNA collection and/or specimen storage at Screening or any time during the study up to and including the EOS visit.

With the subject's approval and as approved by local IRBs, de-identified biological samples will be stored at a certified, licensed central laboratory. These samples may be used to research the causes of CRSwNP, its complications and other conditions for which individuals with CRSwNP and asthma are at increased risk, and to improve treatment. The central lab will also be provided with a code-link that will

allow linking the biological specimens with the phenotypic data from each subject, maintaining the blinding of the identity of the subject.

During the conduct of the study, a subject may choose to withdraw consent to have biological specimens stored for future research.

Once samples have been analyzed specimens will be destroyed. If no analyses have been completed within 5 years following EOS, samples will be destroyed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Table 4 lists the key personnel for this study. Additional study contact information will be provided in the Study Operations Manual.

Table 4. Key Study Personnel for Protocol ANB020-006

10.1.6 DATA AND SAFETY MONITORING BOARD

A DSMB, or otherwise called Independent Data Monitoring Committee, will be set up, prior to the first subject being enrolled in the study, as an independent body to review accumulating data in the study. The DSMB is comprised of 3 independent clinicians (2 pulmonologists, 1 ENT specialist) and 1 independent statistician. Members of the DSMB will not be Investigators in the study, and will be free of any conflicts of interest with the Sponsor or study outcome.

The DSMB will periodically examine the safety data emerging from the study and provide its recommendations to the Sponsor. The roles and responsibilities of the DSMB, their operational procedures, and method of communication with Sponsor will be described in a separate DSMB charter.

The first DSMB meeting is expected to occur prior to the Investigators Meeting. A formal review of the accumulating data is planned for every quarter thereafter, unless an ad hoc meeting is required.

10.1.7 CLINICAL MONITORING

All aspects of the study will be monitored by the Sponsor or authorized representatives of the Sponsor according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (ie, Informed Consent Regulations [US 21CFR, Part 50] and IRB regulations [US 21CFR, Part 56.103]). Access to all records, both during the study and after study completion, should be made available to the Sponsor at any time for review and audit to ensure the integrity of the data. The Investigator must notify Sponsor immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The Investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data are not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Before study initiation, at a study center initiation visit or at a meeting with the Investigator(s), a representative from the Sponsor will review the protocol and study eCRFs with the Investigator(s) and their staff. During the study, the study monitor will visit the study center regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the IP is being stored, dispensed and accounted for according to specifications. The Investigator and key trial personnel must be available to assist the monitor during these visits.

The Investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan.

The Investigator must promptly complete the eCRFs after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the IB, and any protocol amendments.

The Investigator must provide the Sponsor and the responsible IRB with a study summary shortly after study completion, or as designated by the Sponsor.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical study center will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a study center's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, GLP, Good Manufacturing Practices [GMP]).

The study center will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All protocol-specified data will be recorded in the source documents, and data will be entered on the eCRFs from the source documents. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the study, the Investigator will sign a statement indicating that all pages of the subject's case report have been reviewed. Signature stamps and "per signatures" are not acceptable.

It is Sponsor's policy that the study data be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to Screening.

Checks will be performed to ensure the quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the Investigator or study coordinator. Data queries, documented on data query forms, will be sent to the research facility. Site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All unused Sponsor source documents and binders must be returned to the Sponsor upon completion of the study.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Date of birth
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- IP administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (eg, laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to the Sponsor. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The Investigator will ensure that the study documents forwarded to the Sponsor, and any other documents, contain no mention of subject names.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate) and countersigned by the Investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The Investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Regulatory authorities, the IRB and/or the Sponsor's Quality Assurance group (or designee) may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. The Investigator must guarantee direct access to these documents. eCRFs will be kept by the Sponsor or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file

kept by the Sponsor after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the Investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

The Investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and relevant regulatory agencies. If the Investigator withdraws from the study (eg, relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to the Sponsor in writing.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or MOP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the study center Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP, Clinical Monitoring Plan, Medical Management Plan, and SAP.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the medical monitor and the Sponsor at the earliest

possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the medical monitor.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 5 years after the completion of the primary endpoint by contacting the Sponsor.

It is understood by the Investigator that the information generated in this study will be used by Sponsor in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

Any results of medical investigations with Sponsor's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Investigator and Sponsor representative(s) 30 days before submission for publication or presentation. Due regard shall be given to Sponsor's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. The Sponsor shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual Investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating Investigators and the prior review of the Sponsor.

In case of disagreement among the Investigators participating in a multicenter investigation, the Sponsor will be the final arbiter. Comments shall be given without undue delay. If they are not accepted, the senior author of the manuscript and representatives of the Sponsor shall promptly meet to discuss further and endeavor to agree mutually on the final wording and/or disposition of the publication. The

above procedure also applies to information on prematurely discontinued and other non-completed studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (ie, author and reference).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All persons with direct financial interest in this trial are prohibited to have direct involvement.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 ETHICS AND RESPONSIBLITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, the Declaration of Helsinki, IRB requirements, and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and ICF by an HHS-registered IRB) to the Sponsor before IP will be shipped to the study site.

10.2.2 AMENDMENT POLICY

Only the Sponsor may modify the protocol. Protocol amendments will be made after consultation between the Sponsor and the Investigator(s). Amendments must be approved by all applicable national and local committees including, but not limited to, the government regulatory authorities and/or regional IRB before implementation. The only exception is when an Investigator considers that a subject may be harmed and immediate action] is necessary. Under these circumstances, approval of the chairman of the IRB, or an authorized designee, must be sought immediately. The Investigator should inform the Sponsor, and the full IRB, no later than 5 working days after the emergency occurs.

Protocol-specified safety reporting requirements must be adhered to independent of any other variables. All amendments that have an impact on subject risk, the study objectives or that require revision of the informed consent document must be approved by the IRB before implementation. Administrative changes to the protocol and/or changes that do not impact subject safety, risk, or

comfort may be implemented prior to IRB approval if local institutional policy permits. A copy of the written approval of the IRB, which becomes part of the essential study documents file, must be given to the study monitor. Examples of amendments requiring such approval are:

- A significant change in the study design
- An increase in the number of invasive procedures to which subjects are exposed
- An addition or deletion of a test procedure

The PI at each study center must sign the Investigator's Agreement page of the amended protocol.

10.3 ABBREVIATIONS

ACQ-7	7-Item Asthma Control Questionnaire
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AERD	Aspirin-exacerbated respiratory disease
$AUC_{[tau]}$	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CT	Computed tomography
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report forms
EOS	End of study
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EQ-5D	EuroQoL-5D Scale
ETV	Early termination visit
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgE	Immunoglobulin E
INCS	Intranasal corticosteroid
IND	Investigational New Drug Application

IP	Investigational product
IRB	Institutional Review Board
IXRS	Interactive Web Response System
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	Mometasone furoate nasal spray
MMRM	Mixed effects model with repeated measures
NCT	National Clinical Trial
NMAR	Not missing at random
NP	Nasal polyposis
NPIF	Nasal peak inspiratory flow
NPS	Nasal Polyp Score
OCS	Oral corticosteroids
OHRP	Office for Human Research Protections
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per protocol
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QC	Quality control
QoL	Quality of life
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SF-36	Short Form 36 Health Survey
SNOT-22	Sino-Nasal Outcome Test
SoA	Schedule of Activities
SOC	System organ class
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent terminal half-life
TCA	Tricyclic antidepressant drugs
TEAE	Treatment-emergent adverse event
TB	Tuberculosis
Th2	T helper type 2
t_{max}	Time of maximum concentration
UP	Unanticipated problem
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VAS	Visual Analogue Scale
Vd/F	Apparent volume of distribution
WOCBP	Woman of childbearing potential

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
Original Protocol	21 September 2018		
Amendment 1	15 February 2019	Administrative corrections, updated Inclusion/exclusion criteria, clarified procedures. See Summary of Changes for complete summary.	Improving patient safety, aligning criteria in patients enrollment, and improving protocol based on input provided by DSMB and participating clinical Investigators with strong patient management experience.
Amendment 2	15 August 2019	Updated inclusion/exclusion criteria; clarified procedures; updates on statistical considerations, dropout rate and sample size; administrative corrections. See Summary of Changes for complete summary.	Providing clarification, improving patient safety and improving protocol based on input provided by participating clinical Investigators with strong patient management experience.
Amendment 3	06 February 2020	Corrected inconsistencies in objectives and endpoints listed throughout the document and corrected administrative errors.	The synopsis, Section 3, and statistical sections were not consistent for the objectives and endpoints listed.

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APPENDICES

APPENDIX A: PROHIBITED MEDICATIONS AND THERAPIES DURING THE COURSE OF THE STUDY

Excluded medications/therapies are listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF. **The following medications will not be permitted during the study:**

- Biologics, monoclonal antibodies including but not limited to: anti-immunoglobulin E (IgE) therapy (omalizumab), anti-IL-5 therapy (mepolizumab, benralizumab) anti-IL-4/13 (dupilumab)
- Any immunosuppressive treatment including but not limited to: methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide
- Aspirin or nonsteroidal anti-inflammatory (NSAID) in patients with hypersensitivity to aspirin or NSAID
- Systemic corticosteroid
- Decongestion (topical or systemic) is not allowed, except before endoscopy
- Long term use of systemic antibiotics (for 2 weeks or more)
- Lipoxygenase inhibitors
- Use of intranasal medication that could interfere with the symptoms of diseases are prohibited (this includes but is not limited to: chronic use of INCSs, antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn)
- Chronic use of nasal antihistamines within 8 weeks of Screening is prohibited (however acute episodic use within 8 weeks of Screening is permitted. Oral antihistamines and nasal saline are permitted both during Screening and while on-study).
- Polypectomy (allowed as part of medical history up to 3 months prior to randomization)

APPENDIX B: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.

   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):
  - Are abstinent from penile vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile vaginal intercourse with a WOCBP who is not currently pregnant.
  - In addition, male subjects must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 3 months after the last dose of study treatment.

Female Subjects

- Female subjects must refrain from donating ova for the duration of the study and for 3 months after the last dose of study treatment.
- Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device. • Intrauterine hormone-releasing system. Hormone-free intrauterine device interfering with sperm transport and fertilization. Bilateral tubal occlusion or ligation.
Vasectomized Partner A vasectomy is a highly effective birth control method provided that the vasectomized partner is the sole male sexual partner of the WOCBP and the absence of sperm post vasectomy has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Pregnancy Testing

- Women of child bearing potential should only be included after a confirmed menstrual negative highly sensitive SPT at Screening and UPT on Day 1 (prior to study treatment administration).
- Additional pregnancy testing should be performed as mentioned in the SOA (see Section 1.3).
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive UPT result should be confirmed with a serum test.

Collection of Pregnancy Information

Male Subjects with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- The Investigator will record pregnancy information on the appropriate pregnancy form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.6.6. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

APPENDIX C: PHARMACOKINETIC AND ANTI-DRUG ANTIBODY COLLECTION TIMEPOINTS

Study Day	Study Visit	PK Sample Time Point (Serum)	Sample Time Point for ADA
Day 1/Week 0 etokimab/Placebo dosing	2	Predose	Predose
Day 5/Week 1	3	Must occur 3 to 5 days after Day 1 dosing (Visit 2)	
Day 29/Week4	5	Predose	Predose
Day 57/Week 8	6	Predose	Predose
Day 85/Week 12	7	Predose	Predose
Day 113/Week 16	8	PK can be pulled at any time during the study visit	
Day 141/Week 20	9	Anytime during the study visit	Anytime during the study visit
Day 169/Week 24/EOS/ET	10	Anytime during the study visit	Anytime during the study visit

Abbreviation: ADA = Anti-drug antibody; EOS = End of study; ETV = Early termination visit and PK=Pharmacokinetic

APPENDIX D: SAMPLE ENDOSCOPIC NASAL POLYP SCORE

Sample Endoscopic Nasal Polyp Score

Polyp Score	Polyp Size
0	No polyps
1	Polyps in the middle meatus not reaching below the lower border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Polyps causing complete obstruction of the inferior nasal cavity
Total NPS Score:	NPS Left _____ + NPS Right _____ = Total _____

The NPS score is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. NP is graded based on polyp size described in the table above.

APPENDIX E: SAMPLE 22-ITEM SINO-NASAL OUTCOME TEST (SNOT-22)

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

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

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

APPENDIX F: SAMPLE SHORT FORM 36 HEALTH SURVEY (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

APPENDIX G: SAMPLE EUROQOL-5D (EQ-5D)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

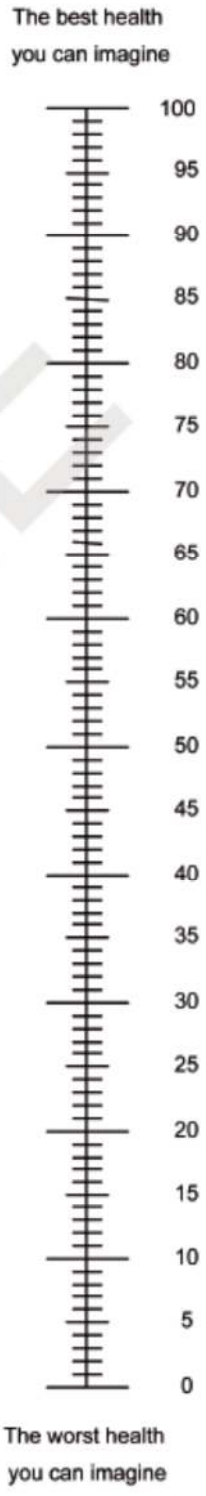
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX H: SAMPLE 7-ITEM ASTHMA CONTROL QUESTIONNAIRE (ACQ-7)

7-ITEM ASTHMA CONTROL QUESTIONNAIRE (ACQ-7)

Please answer questions 1to 6. Circle the number of the response that best describes how you have been during the past week

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few minutes 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6.	On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0 None 1 1-2 puffs most days 2 3-4 puffs most days 3 5-8 puffs most days 4 9-12 puffs most days 5 13-16 puffs most days 6 More than 16 puffs most days

To be completed by a member of the clinic staff

7.	FEV_1 pre-bronchodilator:.....	0	>95% predicted
		1	95-90%
	FEV_1 predicted.....	2	89-80%
	FEV_1 % predicted.....	3	79-70%
	(Record actual values on the dotted lines	4	69-60%
	and score the FEV_1 % predicted in the next	5	59-50%
	column)	6	< 50% predicted

APPENDIX I: SAMPLE NASAL POLYP RELATED RESOURCE USE QUESTIONNAIRE

NASAL POLYP RELATED RESOURCE USE Questionnaire

This questionnaire will record information regarding resource use, including healthcare and work related, for nasal polyps.

Employment status
Check one primary category (Excluding charity activity)

Employed:
☐ Full time
☐ Part time *Please specify time in %:*_____
(Example: an half-time = 50%)

Non-Employed:
☐ Unemployed (Including housewife, student,…)
☐ Retired

NASAL POLYPS-RELATED RESOURCE USE

Please describe resources associated to **nasal polyps that occurred in the past 4 weeks**

OUTPATIENT VISITS

In the past 4 weeks, how many outpatient visits did the patient have by a physician or another healthcare professional for his nasal polyps (other than the planned visits of the protocol)?

General Practitioner _ _
Otolaryngologist (ENT specialist) _ _
Allergist _ _
Internist _ _
Nurse _ _
Other _ _ Please specify: _____
ER visit related to NP _ _

SICK LEAVES / DAYS OFF

If the patient is Employed (Full time or Part time), please complete both questions 1 and 2
If the patient is Unemployed or Retired, please complete the question 2 only

1- **In the past 4 weeks, if the patient is Employed**, how many days did the patient **miss from work due to nasal polyps**:

_ _ . _ days (1/2 days = 0.5 days)

Please specify the reason(s):

☐ Breathing difficulties
☐ Fatigue
☐ Depression / Anxiety
☐ Other *Please specify the main reason:* _____

2- **In the past 4 weeks**, how many days did the patient approximately **miss from his/her usual activities other than work due to nasal polyps**:

_ _ . _ days (1/2 days = 0.5 days)

Please specify the reason(s):

☐ Breathing difficulties
☐ Fatigue
☐ Depression / Anxiety
☐ Other *Please specify the main reason:* _____

APPENDIX J: SAMPLE VISUAL ANALOGUE SCALE