[redacted]

Statistical Analysis Plan for Interventional Studies

Sponsor Name: AnaptysBio Inc.

Protocol Number: ANB020-006
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 Version and Date: Amendment3_v.4.0 (28-Feb-2020)

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REVISION HISTORY

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V1.0	03Apr2020	[redacted]	Added: ACQ-5 analysis. Updated: Nocturnal awaking analysis based on eDiary data, not from ACQ-7. Administration changes: updated sponsor reviewer, minor changes throughout.

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

Approvals

[redacted] **pproval**

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Sponsor Approvals

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[redacted]	Signature	Date (DD-MMM-YYYY)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ACQ-7	7-Item Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse Event
AERD	Aspirin-exacerbated respiratory disease
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
$AUC_{[0\text{-}infin]}$	Area under the concentration-time curve from Time 0 extrapolated to infinity
$AUC_{[0\text{-}last]}$	Area under the concentration-time curve from time 0 to the time of the last Quantifiable concentration
$AUC_{[tau]}$	Area under the concentration-time curve from time 0 to Tau where Tau is the dosing interval
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRF	Case Report Form
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report forms
EOS	End of study
EOT	End of treatment

Abbreviation	Description
ePRO	Electronic subject reported outcome
EQ-5D	EuroQoL-5D Scale
ETV	Early termination visit
FAS	Full analysis set
FEV_1	Forced expiratory volume
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IA	Interim Analysis
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
INCS	Intranasal corticosteroid
IP	Investigational product
IXRS	Interactive Web Response System
LFTs	Liver Function Tests
mAb	Monoclonal antibody
MAR	Missing at Random
Max	Maximum
MCAR	Missing Completely at Random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	Mometasone furoate nasal spray
Min	Minimum
MMRM	Mixed effects model with repeated measures
MOP	Manual of Procedures
N/A	Not Applicable

Abbreviation	Description
NA	Not Applicable
NMAR	Not missing at random
NP	Nasal polyposis
NPIF	Nasal peak inspiratory flow
NPS	Nasal polyp score
OCS	Oral corticosteroids
PI	Principal investigator
PK	Pharmacokinetics
PP	Per protocol
PR	Pulse rate
PT	Preferred Term
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QC	Quality Control
QoL	Quality of life
QTc	Corrected QT Interval
QTcF	QT corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form 36 Health Survey
SI	Standard International System of Units
SNOT-22	Sino-Nasal Outcome Test
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

Abbreviation	Description
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment-emergent Adverse Event
TB	Tuberculosis
TFL	Tables, Figures, and Listings
t_{max}	Time of maximum concentration
ULN	Upper Limit Normal
TTFR	Time to First Response
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
VAS	Visual Analogue Scale
Vd/F	Apparent volume of distribution
VMSOD	Volumetric Maxillary Sinus Occupied by Disease
WHO	World Health Organization
WOCBP	Woman of childbearing potential

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses that will be performed and to ensure that data listings, summary tables and figures which will be produced, and the statistical methodology that will be used, are prespecified, complete and appropriate to allow valid conclusions regarding the study objectives. This version of the SAP is based on Amendment 3 of the Protocol, dated 06 February 2020.

2.1. Responsibilities

[redacted] ill perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings. Pharmacokinetic analysis will be primarily carried out by an appropriately designated vendor assigned by AnaptysBio Inc. [redacted] will provide listings and figures of PK concentrations.

2.2. Timings of Analyses

The primary analysis of safety, tolerability, efficacy and/or pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study, the database is locked, evaluability decisions are made, and the treatment identifiers unblinded.

An independent Data and Safety Monitoring Board (DSMB), or otherwise called Independent Data Monitoring Committee (IDMC), will review accumulating safety data periodically during the study. An independent unmasked team from [redacted] biostatistics will perform the analyses to maintain the masking of the study. Analyses for the DSMB are described in a separate DSMB SAP.

An interim analysis (IA) is planned when approximately 84 randomized subjects have completed Week 8 of the study. The results of the IA will be used, by designated AnaptysBio personnel (employees and/or consultants) without direct contact with the sites, to make decisions for a Phase 3 program and determine the likelihood for further etokimab clinical development in other indications. An unblinded team from [redacted] biostatistics will perform the analyses as described in Section 3.7 of this SAP (refer to blinding tain the blinding of the study).

3. STUDY OBJECTIVES

3.1. 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).

3.2. Secondary Objective(s)

To evaluate:

- Effectiveness of etokimab compared to placebo in subjects with CRSwNP in relieving clinical symptoms.
- Safety and tolerability of etokimab in subjects with CRSwNP compared to placebo following a 16-week treatment period.
- Pharmacokinetics (PK) of etokimab in human serum in subjects with CRSwNP following subcutaneous (SC) administration.

3.3. Exploratory Objective(s)

To evaluate:

- Improvement in Quality of Life (QoL) in subjects with CRSwNP treated with etokimab compared to placebo following a 16-week treatment period.
- Other effects of etokimab compared to placebo in subjects with CRSwNP following a 16-week treatment period.

3.4. Brief Description

The current study, ANB020-006, is a randomized, double blind, placebo controlled, parallel group, multiple dose, Phase 2 study designed to assess efficacy, safety, tolerability, and PK of two different doses and dose regimens of etokimab following a 16-week treatment period compared to placebo in adults with moderate to severe CRSwNP.

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 medication on Day 1; a 16-week treatment period (Week 0 to Week 16); and an 8-week safety follow-up period. The total participant duration will be approximately 28 weeks.

During the screening period, all subjects will undergo evaluation for eligibility. Randomization will be stratified by a subject's asthma comorbidity: yes/no. The subjects will be randomly assigned on Day 1 to 1 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 medication 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 each study medication 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)/end of study (EOS).

3.5. Subject Selection

Eligibility for study participation is based on the inclusion and exclusion criteria in the following sections.

3.5.1. 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 nasal polyp score of 4 out of 8 (maximum score), with minimum of 1 in each nostril, despite completion of a prior intranasal corticosteroid (INCS) treatment for 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 woman of childbearing potential (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 (e.g., hormonal contraception should be initiated at least 28 days before Study Day 1).
6. Screening laboratory values must meet the following criteria:
    a. AST and ALT levels ≤ 3 x ULN
    b. Total Bilirubin ≤ 1.5 x ULN

c. Albumin ≥ 3 g/dL - Lipase ≤ 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 informed consent form (ICF).
8. Subject must use mometasone furoate nasal spray (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).

3.5.2. Exclusion Criteria

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

1. Prior exposure to etokimab.
2. SNOT-22 score ≤ 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 oral corticosteroids (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 ≥ 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 polysorbate 80, 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 (e.g., 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) (i.e. 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 co-morbidity that the investigator believes is a contraindication to study participation. This includes, but is not limited to, any respiratory (e.g., 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 and 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 condition 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 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 (e.g. 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.

3.6. Determination of Sample Size

The two co-primary endpoints were assessed in order to determine the sample size that will provide adequate power to detect a clinically meaningful difference between each etokimab dosing regimen and placebo.

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

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 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 three 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.

Each co-primary endpoint will will be tested against two-sided alpha=0.05; therefore, the combined power for the tesing of both endpoints is approximately 80%, assuming no negative correlation between endpoints.

3.7. Treatment Assignment & Blinding

Eligible subjects will be randomized on Day 1 to 1 of 3 treatment arms in a 1:1:1 ratio based on a computer-generated centralized randomization schedule prepared under the supervision of the sponsor.

- Arm 1 (Eto Q8W): Etokimab 300 mg load + 150 mg SC every 4 weeks (Weeks 0, 4, 8, and 12)

- Arm 2 (Eto Q4W): Etokimab 300 mg load + 150 mg SC every 8 weeks (Weeks 0 and 8) and placebo (Weeks 4 and 12)
- Arm 3 (Placebo): (Weeks 0, 4, 8, and 12)

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 medication 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 medication.

Study medication is provided as 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

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 and electronic case report form (eCRF), as applicable.

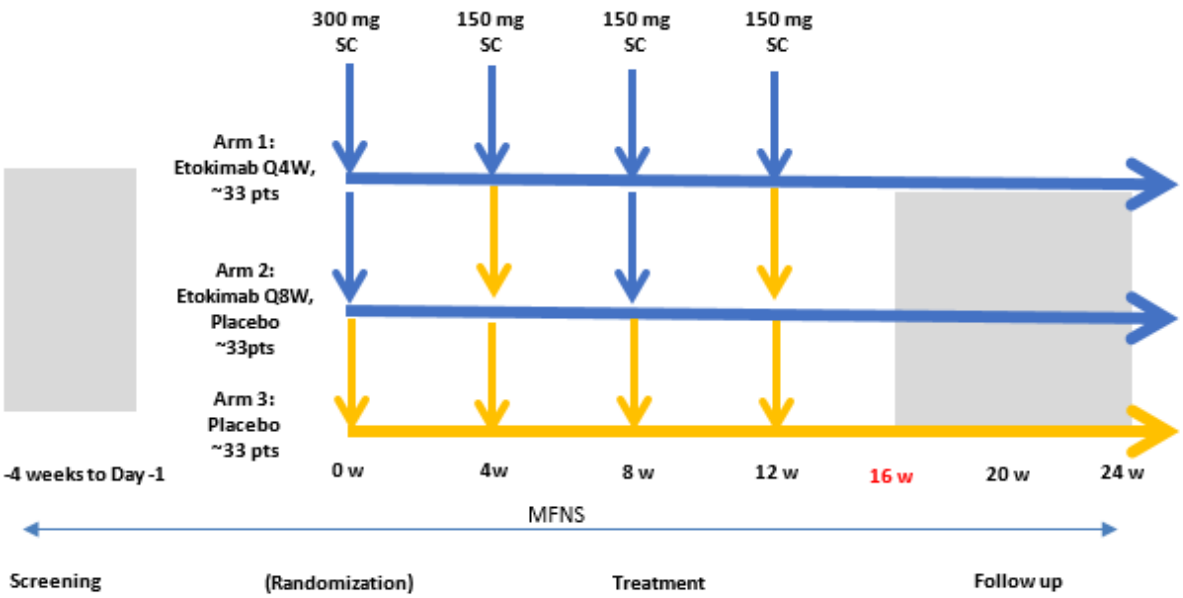
An unblinded statistician and statistical programmer separate from the study team will be responsible for providing unblinded reports to the DSMB, for presentation of the unblinded reports for the formal interim analysis, and for handling unblinded PK and other data (e.g. eosinophils) that may potentially unblind the study. Data import agreements will provide for protections from revelation of unblinded subject information.
[redacted] maintains a restricted area within its programming environment that will not be accessed
el associated with routine handling of study information.

3.8. Administration of Study Medication

Study medication will be administered SC during onsite visits (Visits 2, 4, 5, and 6) on Study Day 1 (Week 0), Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

The dosing regimens are illustrated in the following diagram:

Figure 1. **Study Schema for Protocol ANB020-006**



Legend:

Etokimab = blue line

Placebo = yellow line

Primary endpoints assessed = red type

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

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, Study 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.

3.9. Study Procedures and Flowchart

Table 1: Schedule of Activities

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		

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[a]	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
ePRO Device Dispensation/Collection[n]		X							X
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.

* 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

[redacted]

4. ENDPOINTS

4.1. Primary Efficacy Endpoint

Associated with the primary efficacy objective to evaluate the efficacy of etokimab compared to placebo in subjects with CRSwNP following a 16-week treatment period are the following two 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

4.2. Secondary Efficacy Endpoints

Secondary endpoints identified in the protocol are listed below:

- Time to first response (≥ 1 point improvement) in NPS
- NPS response defined as a reduction of at least 1.0 from baseline to Week 16 in NPS
- SNOT-22 response defined as a reduction of at least 12.0 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)

4.3. Exploratory Endpoints

Exploratory endpoints identified in the protocol are:

4.3.1. Quality of Life (QoL)

- 36-item Short Form Health Survey (SF-36)
- European QoL scale (EQ-5D)
- Patient-related rhinosinusitis symptoms severity using a visual analog scale (VAS)
- Number of nocturnal awakenings

4.3.2. Other effects

- 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 SNOT-22 scores in subjects with comorbid asthma
- Percent change from baseline in 3-dimensional volumetric measurement of the maxillary sinus as assessed by CT scan
- Change from baseline to Week 16 in forced expiratory volume (FEV1) (overall and in subgroup with asthma)

- Change from baseline to Week 16 in FEV1 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
- Time to study treatment discontinuation
- Incidence of treatment discontinuation due to need for OCS or nasal polyp surgery
- Change in Nasal Polyp Resource Questionnaire from baseline to Week 16

4.4. Pharmacokinetic Endpoints

Pharmacokinetic endpoints are as follows:

A limited sampling strategy to collect samples of whole blood was implemented for the determination of etokimab concentrations in human serum for PK assessment following subcutaneous (SC) administration.

The PK endpoints for this study are as follows:

- Primary PK parameters
  - Apparent clearance (CL/F) of etokimab
  - Apparent volume of distribution (Vd/F) of etokimab
- Secondary PK parameters
  - Area under the curve (AUC_{τ}) for the first and last dose
  - Maximum concentration (C_{max}) for the first and last dose
  - T_{max} (Time of maximum concentration) for the first and last dose
  - $t_{1/2}$ (apparent terminal half-life) for the last dose after SC dosing if possible

4.5. Safety Endpoints

Outcome measures are listed below:

- 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 [PR])
- Changes in electrocardiogram (ECG) parameters
- Immunogenicity (anti-drug antibody [ADA] and neutralizing ADA)

5. ANALYSIS SETS

5.1. Enrolled Set

The Enrolled Set will include all subjects who gave informed consent and were enrolled in the study. Unless specified otherwise, this set will be used for subject listings and summaries of subject disposition.

5.2. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who receive at least 1 dose of etokimab or placebo. The Safety Analysis Set will be used for all safety analyses. Subjects will be analyzed according to treatment received. Unless specified otherwise, this set will be also used for subject listings and summaries of safety endpoints.

5.3. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who receive at least 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. Subjects will be analyzed according to randomized treatment. Unless specified otherwise, this set will be also used for subject listings and summaries for all efficacy analyses.

5.4. Per Protocol (PP) Analysis Set

The 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. The PP analysis set will be used only for the supplementary analysis of co-primary endpoints. Subjects will be analyzed according to their randomized treatment.

Subject assignments to the PP Analysis Set will be determined after blinded data review to assess major protocol deviations necessitating exclusion from the PP Analysis Set prior to any unblinding of treatments for formal statistical analysis. Major protocol deviations are defined in Section 7.3.

5.5. Pharmacokinetic (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 protocol deviations or events with the potential to affect PK concentrations. The PK Analysis Set will be used for all PK analyses and listings of PK concentration data.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

The following conventions will be utilized in the analyses:

- The final statistical analysis will not be performed until all the reportable data have been collected, queries answered, and the database locked.
- All relevant individual subject data will be provided in data listings sorted by treatment arm and subject number. The following treatment group labels will be used: "Placebo", "etokimab Q8W", and "etokimab Q4W". Where subjects who were not randomized are included in listings, the treatment arm will be indicated as "Not Assigned" or "Not Randomized".
- Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. All tabular summaries will be presented by treatment arm as indicated above. A total column may be included under "All Subjects" where necessary or appropriate.
- In general, continuous variables will be summarized by descriptive statistics including the number of observations (n), mean, standard deviation (SD) or standard error (SE), median, minimum (min), and maximum (max); the lower (Q_1) and upper quartile (Q_3) may be included in some summaries if deemed necessary or important. The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean, median, lower and upper quartiles and 2 more decimal places than in the raw data will be presented when reporting SD or SE.
- Categorical data will be summarized using the number of observations (n), frequency, and percentage of subjects in the relevant analysis set and treatment group falling within each category.
- Unless otherwise specified, where there are multiple measurements at a post-baseline visit or time of assessment, the value closest to the target date within the specified window for the assessment visit will be used for analysis.
- For numerical variables, change from baseline will be calculated as the value of interest at the time of measurement minus the corresponding baseline value.
- All statistical tests will be two-sided; unless otherwise indicated; two-sided p-values < 0.05 will be regarded as statistically significant, and confidence intervals (CI) will be 2-sided and have 95% confidence level.
- All subject data will be included in listings.
- Data analyses will be conducted using validated computer software (e.g. SAS® Version 9.4 or higher).
- Adverse events will be coded using the most recent MedDRA version 21.0 or higher.
- Concomitant medications will be coded using the most recent version of World Health Organization (WHO) -DDE version March 2018 or later.
- In this SAP, we will designate the treatment arms as Placebo, etokimab Q4W, and etokimab Q8W. In data presentations, etokimab Q4W will be in the 1st column, etokimab Q8W in the 2nd column, and the Placebo group in the 3rd column.

6.2. Key Definitions

6.2.1. Baseline

Unless otherwise specified, "baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study medication (this includes unscheduled visits). Definitions of baseline for specific efficacy and/or safety parameters are provided in relevant sections where those parameters are defined and their analysis methods described.

For numerical variables, change from baseline will be calculated as the value of interest at the time of measurement minus the corresponding baseline value.

6.2.2. Study Day

The first dose date is defined as the date the first dose of study medication was received after the subject was randomized. Study medication is expected to be administered in the pharmacy on Study Day 1, the randomization visit date, also the same as the Visit 2 date. In the protocol, reference to Week 0 may be regarded as Study Day 1. Study days used in the subject listings are calculated from Study Day 1.

For Study days on or after the date of treatment start, Study Day will be calculated as:

Study day = Assessment date – First dose date + 1

For study days prior to dosing, Study Day will be calculated as:

Study day = Assessment date – First dose date

There is no Study Day 0.

6.2.3. Study Periods

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

Period	Start	End
Screening/Baseline	Visit 1 date	Day 1 (Visit 2) date - 1
Treatment Period	Day 1 (Visit 2 date)	Visit 7/EOT date - 1
Safety Follow-up	Visit 7/EOT date	Visit 9/EOS date

Day 1 is Week 0.

6.3. Missing Data

6.3.1. Birth Dates

Birth date may not be needed, if the age is provided. However, in case the birth date is needed for calculation, if the date of birth is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will not be presented in the data listings.

6.3.2. Medical History Diagnosis Dates

If the onset date of any medical history diagnosis is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will be used to derive study day and will not be presented in the data listings. Any missing dates will be presented as "UNK" in the listing.

6.3.3. Medication Dates

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only. Imputed dates will not be presented in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the first dose date, the medication start day will be imputed as the day of first dose. Otherwise, the first of the month will be used.
- If month is missing and the year matches the year of the first dose date, the medication start month and day will be imputed as the month and the day of the first dose date. Otherwise, January 01 will be used.
- If the start date is completely missing, the start date will not be imputed.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- If the day is missing, then the last day of the month will be used.
- If the month and day are missing, then December 31 will be used.
- If the stop date is completely missing then the date of last study participation date will be used.

6.3.4. Adverse Events

6.3.4.1. *Missing dates*

The following rules will be used to impute start and/or stop dates for adverse events with incomplete dates, in order to determine whether an AE is treatment-emergent or not. Imputed dates will not appear in the data listings.

Adverse events with partial start dates:

- If AE start day is missing, and the month and year match the month and the year of the first dose date, the day of the first dose date will be imputed. Otherwise, the first of the month will be used.
- If AE start month is missing, and the year matches the year of the first dose date, the month and the day of the first dose date will be imputed. Otherwise, January 01 will be used.
- If the AE start date is completely missing, the AE will be imputed to the first dose date.

- If the AE stop date is complete and the imputed AE start date is after the AE actual stop date, then the AE start date will be imputed as January 01 of the same year as the AE stop date.

6.3.4.2. *Other missing information*

Any missing severity assessments for AEs will be imputed as "severe" and any missing relationship to study medication will be considered "related" for summary purposes. The imputed values will not be presented in the listing.

6.3.5. Efficacy Assessments

Missing data may arise due to subjects missing some assessments (intermittent missingness), or as a result of subject dropouts and not being available for subsequent assessments (monotone missingness).

The primary analysis via the general linear model with random effects (also called Mixed Model with Repeated Measures (MMRM)) uses all available data and assumes that the missing data due to dropouts are missing at random (MAR). The Kenward Roger method is used to calculate the denominator degress of freedom and adjust standard errors for the test of fixed effects. In order to assess the impact of missing data due to dropouts on the inference for the co-primary endpoints, a sensitivity analysis will be performed where data after dropout will be imputed using multiple imputation and the statistical analysis via MMRM will be repeated with the filled in data. Details on the multiple imputation is described in Section 8.1.1.3.

6.4. Visit Windows

All data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). The unscheduled, end-of-treatment (EOT) and early termination (ET) visit will be mapped to a scheduled visit for analysis using the date of collection/assessment and Day 1, first dose date, as a basis to determine study day and then study day will be mapped to the intended visit according to the visit windows specified in the table below. Unscheduled visits after EOT visit date, including ET visit, will be windowed using relative days since last dose date; the mapping will follow the table below. In order to accommodate as much data as possible into analysis, these windows have been widened compared to protocol-specified operational window, to have no gap between them (exception: UPSIT, Lund-MacKay scores; See Table 2e); these windows are used for analyses purpose only. Data collected weekly (i.e., EQ-VAS) or daily (i.e., nocturnal awakenings, nasal peak inspiratory flow [NPIF]) will be mapped to the analysis week starting from Day 1, Week 1 through Week 24 using the date of collection/assessment.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the "analyzed record" within the analysis window. A subject's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If there is a scheduled visit/day for the analysis visit window, then the scheduled visit/day data will be used.
- If there is no scheduled visit/day for the analysis visit window, the data closest to the scheduled day/time (i.e., target day) will be used. Exception: Week 24/EOS/ETV visit will use the last observation in the visit window, instead of the closest data.

- If there is no scheduled visit/day for the analysis visit window and there is a tie between the data in the number of days/hours before and after the scheduled day, the later data will be used.

The summary by visit will use "analyzed records" only ---at most one per subject per parameter.

An unscheduled visit that does not fall under any window will remain in the database and will be included in the listings. The data not flagged as the "analyzed record" will be included in subject listings. Tables 2a to 2f display visit windows for multiple analyses.

Table 2a: Visit Windows for Assigning ET Visits to an Analysis Visit for Nasal Endoscopy, SNOT-22, QoL, Nasal Polyps Resource Questionnaire, and ACQ-7

Study Period	Analysis Visit	Target Day	Window for Reassignment to Analysis Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 4	29	2-42
	Week 8	57	43-70
	Week 12	85	71-98
	Week 16/EOT	113	99-126
Safety Follow-up Period	Week 24/EOS/ETV**	169	127-182

**The last observation in the time window will be used. *[This is an exception from the rule regarding closest to target.]*

Table 2b: Visit Windows for Assigning ET Visits to an Analysis Visit for Spirometry

Study Period	Analysis Visit	Target Day	Window for Reassignment to Analysis Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 4	29	2-42
	Week 8	57	43-70
	Week 12	85	71-98
	Week 16/EOT**	113	99-126

**The last observation in the time window will be used. *[This is an exception from the rule regarding closest to target.]*

Table 2c: Visit Windows for Assigning ET Visits to an Analysis Visit for Hematology and Chemistry

Study Period	Analysis Visit	Target Day	Window for Reassignment to Scheduled Analysis Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 1	5	2-10
	Week 4	29	11-42
	Week 8	57	43-70
	Week 12	85	71-98
	Week 16	113	99-126
Safety Follow-up Period	Week 24/EOS/ETV**	169	155-182

**The last observation in the time window will be used. *[This is an exception from the rule regarding closest to target.]*

Table 2d: Visit Windows for Assigning PW Visits to an Analysis Visit for Immunogenicity and Vital Signs

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 4	29	2-42
	Week 8	57	43-70
	Week 12	85	71-98
	Week 16/EOT	113	99-126
Safety Follow-up Period	Week 20	141	127-154
	Week 24/EOS/ETV**	169	155-182

**The last observation in the time window will be used. *[This is an exception from the rule regarding closest to target.]*

Table 2e: Visit Windows for Assigning PW Visits to an Analysis Visit for UPSIT and Lund-MacKay Scores

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 8*	57	43-84
	Week 16/EOT	113	85-126

*UPSIT only. Lund-MacKay score is not assessed at Week 8.
**UPSIT and Lund-MacKay scores do allow gaps between analysis visits.

Table 2f: Visit Windows for Assigning PW Visits to an Analysis Visit for EQ-VAS, Nocturnal Awakenings, and NPIF

Study Period	Visit	Target Day*	Window for Reassignment to Scheduled Visit
Baseline	Baseline	1	≤1
Treatment Period	Week 1	5	2-7
	Week 2	11	8-14
	Week 3	18	15-21
	Week 4	25	22-28
	…	…	…
	Week 16/EOT	102	99-105
Safety Follow-up Period	Week 20	130	127-133
	…	…	…
	Week 24/EOS/ETV**	158	155-161

*Except for Week 1, Target Day for the rest weekly analysis visits is the mid-week day.
**The last observation in the time window will be used. *[This is an exception from the rule regarding closest to target.]*

6.5. Pooling of Centers

There are approximately 25 investigative sites participating in the study. It is likely that the number of subjects recruited by each site will be small. The primary analysis will use data pooled across sites. No descriptive summaries by site are planned.

6.6. Subgroups

Randomization was stratified by asthma comorbidity. Hence, statistical analysis will explore treatment differences for the co-primary endpoints in subgroups defined by asthma comorbidity. Specifically, treatment effects will be explored in subjects with and without comorbid asthma.

Among the exploratory efficacy endpoints, changes from baseline in FEV1 and percent predicted FEV1 will be analyzed for asthma subgroup in addition to the overall group, and the ACQ-7 will be analyzed in the asthma subgroup only.

Additional subgroup analyses such as by weight may be performed post-hoc, as needed.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. Subject Disposition and Withdrawals

A summary of subject disposition will be provided including the number of subjects screened, number of screen failures, number randomized, number treated, completed the study as well as the number of subjects who discontinued early from the study. Reasons for early discontinuation from the study will be summarized.

For subjects enrolled but screen failed, the denominator used to calculate the percentage will be the number of enrolled subjects (subjects who have signed the informed concent form). For all other calculations, the denominator will be the number of subjects randomized. Subject disposition will be presented overall and by treatment group.

The number of subjects in each analysis set (Enrolled, FAS, Safety, PP, PK) will also be summarized.

A separate summary will be provided of the number and percentage of subjects attending each visit. Percentages will be based on the FAS. A listing of subject visits will be provided for all subjects.

7.2. Inclusion/Exclusion Criteria

Inclusion/exclusion criteria definitions and violations will be listed for all enrolled subjects. If no inclusion/exclusion violations are reported, this will be noted in place of the listing.

7.3. 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.

In addition to site level deviations, individual subject level protocol deviations may include (but are not limited to) the following. Details of each deviation are specified in the Protocol Deviation and Non-compliance Management Plan.

- Concomitant Medication
- Enrollment Criteria
- Informed Consent
- Dosing
- Non-Compliance
- Regulatory
- Visit Schedule
- Visit/Procedure Required
- Other
- Laboratory

Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

Deviations may be categorized as major or minor. Major deviations will be summarized in a table for Enrolled set. All deviations (major or minor) will be presented in a subject listing sorted by treatment and summarized for Enrolled set.

Major protocol deviations that are thought to affect the evaluation of efficacy and/or safety will lead to exclusion of subjects from the PP Analysis Set. This determination will be made by the sponsor after joint review of all major protocol deviations by the study team prior to unblinding.

7.4. Demographic and Other Baseline Characteristics

The following demographic characteristics will be summarized for the FAS and Safety analysis Sets:

- Age [Years]
- Age category (< 65, ≥ 65 years)
- Sex
- Race
- Ethnicity
- Height [cm]
- Weight [kg]
- BMI [kg/m^2]
- Asthma comorbidity (yes/no)
- Smoking status (never, current, former), Number of cigarettes packs smoked per day
- Child-bearing potential

In case age is not provided in the CRF and needs to be calculated, it will be calculated as:

Age (at Screening = (Informed consent date - date of birth + 1) / 365.25 and truncated to complete years.

Weight will be converted to kilograms (kg) when reported in pounds (lbs) as follows: Weight (in kg) = weight (in lbs) * 0.4536

Height will be converted to centimeters (cm) when reported in inches (in) as follows: Height (in cm) = height (in inches) * 2.54/100

All subject demographics data will be listed for the Enrolled Set.

7.5. Medical History

Medical history information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher, summarized and presented overall and by treatment group for the Safety Analysis Set. Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT).

The number and percentage of subjects will be displayed for each System Organ Class and Preferred Term within treatment group.

A listing of medical history will be presented for the Safety Analysis Set.

7.6. Prior and Concomitant Medication

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) March 2018 or later.

Prior medications are defined as any medication that was stopped prior to the first dose of study medication. Concomitant medications are defined as any medication that is ongoing at the time of the first dose of study medication or is started after the first dose of study medication.

Prior and concomitant medications will be separately summarized by presenting the counts and percentage of subjects with medications/therapies overall and by each treatment group for the Safety Analysis Set. Medications will be summarized and sorted alphabetically by Anatomical Therapeutic Chemical (ATC) categories (ATC level 2 categories) and then by the preferred name within the ATC level 2 category. Subjects will be counted only once for each medication class and each preferred drug name.

Prior and concomitant medications/therapies will be listed together with a designation to identify the medications/procedure as prior and/or concomitant and sorted by start date.

8. EFFICACY

The primary efficacy objective of this study is a comparison of each of two dosing regimens of etokimab with placebo in the treatment of subjects with CRSwNP following a 16-week treatment period (change from baseline using co-primary endpoints). Two co-primary efficacy endpoints will be analyzed.

The analysis of the primary and secondary efficacy parameters will be performed on the FAS, unless otherwise noted. The primary and secondary efficacy analyses will be repeated on the PP analysis set if there are substantial differences between the makeup of the FAS and the PP Analysis Set, in order to assess the impact of major protocol deviations on the key inference.

All primary and secondary efficacy variables will be analyzed for data obtained for the Treatment Period.

8.1. Primary Efficacy Endpoint and Analysis

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

Statistical significance for the co-primary efficacy endpoints will be declared if and only if both 2-sided p-values for the tests of the individual hypotheses are < 0.05. Testing will be conducted in a hierarchical manner for each co-primary endpoint such that the comparison of the etokimab Q4W treatment arm versus placebo will be conducted first. If the result from this test is statistically significant, then the comparison of the etokimab Q8W treatment arm versus placebo will be performed. If the result from the etokimab Q4W versus placebo is not statistically significant, no further testing will be performed for the etokimab Q8W treatment arm versus placebo.

8.1.1. Nasal Endoscopy

Nasal endoscopy is performed acc ording to the schedule of assessments in Table 1, on Day 1, Week 4, Week 8, Week 12, Week 16 and Week 24. Each nostril is scored on a scale of 0 to 4, and hence the total NPS value at each visit is between 0 and 8. For each nostril, a score of 0 means no polyps, while a score of 4 means the presence of polyps causing complete obstruction of the inferior nasal cavity. The NPS value at the screening visit is used to determine qualification for enrollment in the study. The NPS score at Week 24 is for safety follow-up.

If a subject's NPS image is initially evaluated as unreadable, the subject may be asked for a repeat endoscopy. If the original image is taken during the screening period, the subject will be asked to repeat endoscopy. If the original image is during post-randomization, the endoscopy will not be repeated with the exception of the Week 8 and Week 16 images. If the images taken for the Week 8 or Week 16 visits are not readable, every attempt should be made to repeat the procedure as close to the original visit window and the re-taken image will be used for analysis. For analysis purposes, baseline endoscopic score (NPS value) will be defined as the total (left and right) NPS value reported at the last visit on or prior to the first dose date (Day 1). Total NPS values will also

be obtained at each visit during Treatment Period (Week 4, 8, 12 and 16), and at the end of the Safety Follow-up Period (Week 24).

A listing of nasal endoscopy performance, nasal polyp scores, and change from baseline scores will be provided per visit per subject for the Full Analysis set.

8.1.1.1. *Definition of Estimand*

Subjects who permanently stopped the study medication are not required to withdraw from the study. Subjects were informed that if they decided to discontinue study medication, they had the option of providing clinic assessments at scheduled office visits or by phone contact until the planned end of their study visits.

Thus, the (co)primary estimand chosen here is the de facto or treatment policy estimand, which uses the available on-treatment NPS values during Treatment period. The primary time point is Week 16.

The NPS is also measured every 4 weeks during treatment and at end of treatment (Week 16). A general linear mixed model with repeated measures (MMRM) will be used to obtain least squares means of change in NPS at Week 16 from baseline, to compare the etokimab treatment arms with the placebo arm.

Summary statistics for each time point will include n, mean, standard deviation, median, minimum, and maximum, for baseline, each time of measurement, and the change from baseline calculated as post-baseline value minus the baseline value.

8.1.1.2. *Primary Statistical Analysis for NPS*

Statistical analysis of this endpoint will employ a general linear model with repeated measures (also called a mixed model with repeated measures, MMRM), with the change from baseline in NPS as the dependent variable; baseline (Day 1) NPS score as a covariate, treatment group (3 levels), stratification factor, treatment by stratification factor, categorical time points (Weeks 4, 8, 12 and 16) and treatment by time interaction as fixed effect factors, and subject as a random effect in the model. Assuming treatment (trtpn) is coded as Placebo=1, Eto Q8W=2, Eto Q4W=3, and that the time variable (weekn) is ordered as 4, 8, 12, and 16, we can write the SAS model of interest to be performed with SAS PROCEDURE MIXED as follows:

```
PROC MIXED DATA = DATASETNAME;
    CLASS USUBJID WEEKN TRTPN STRAT;
    MODEL CFB = BASE STRAT TRTPN STRAT*TRTPN WEEKN WEEKN*TRTPN / SOLUTION DDFM=KR;
    REPEATED WEEKN / SUBJECT=USUBJID TYPE=UN;
    LSMEANS WEEKN*TRTPN / CL ALPHA=0.05;
RUN;
```

The (co)primary hypothesis to be tested for this estimand is that 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.

This hypothesis will be tested by comparing the least squares adjusted means for each etokimab dose group with placebo, at the week 16 time point. Comparison of each treatment arm with placebo will be based on the change in least squares means at Week 16 obtained from the MMRM. Testing will be conducted in a hierarchical manner such that the comparison of the etokimab Q4W treatment arm versus placebo will be conducted first.

If the results of the comparison of the eetokimab Q4W treatment arm versus placebo are statistically significant, the etokimab Q8W treatment arm will be compared to placebo.

While the treatment group means at each visit are estimated by the model, the standard deviations are nuisance parameters and must also be estimated in order to carry out the hypothesis tests and/or obtain confidence interval estimates for means and contrasts. 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 the model does not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure (TOEPH) will be used instead. In case the model will not converge with the heterogeneous Toeplitz structure, heterogeneous compound symmetry (CSH) will be used instead. The denominator degrees of freedom will be computed using the Kenward-Roger method.

The p-value for the comparison will be obtained and compared to the significance level of 5%, two-sided. 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. Comparison of multiple treatment groups versus placebo will be performed in a hierarchical manner so further adjustment will not be made for testing each dosing regimen with placebo. Statistical significance (two-sided p-value < 0.05) for a treatment contrast will be taken to infer a difference in efficacy versus placebo for that etokimab dosing regimen. The direction of difference will determine whether that dosing regimen of etokimab is better or worse than the placebo group at that specified level of significance.

Graphical displays of the results will be presented. The (by-time point) least squares means and two-sided 95% confidence intervals for each treatment will be plotted against time, and the p-values for the Week 16 comparisons will be displayed on the Week 16 time point.

8.1.1.3. *Supplementary Statistical Analysis for NPS*

In order to assess the impact of missing data due to dropouts on the inference for the co-primary endpoints, a sensitivity analysis will be performed in 2 ways. First, NPS data after dropout will be imputed using multiple imputation and the statistical analysis using MMRM will be repeated. Multiple imputation analyses will be performed based on both Missing at Random (i.e. the missing data are assumed to follow the same model as the other patients in their respective treatment arm) and Missing Not at Random assumptions. Second, an ANCOVA will be performed only for the subjects who have completed Week 16 assessment (ie., completers analysis).

MI analysis with Missing at Random (MAR) assumption: In the analysis of each of the co-primary endpoints, subjects with missing data at post-baseline visits will have data imputed using multiple imputation (MI) methodology using the total study sample. MI will be performed under the assumption of MAR. Intermittent missing value(s) will also be replaced using MI. MI will impute 10 integer values using Markov Chain Monte Carlo (MCMC) methods assuming nonmonotone missing, a pre-specified seed number, 500 burn-in iterations, 100 iterations between imputations, and a non-informative prior. The imputation models based on all subjects (regardless of treatment group) will include the randomization stratification factor, the baseline value of the endpoint, and all previous values of the endpoint at each time point. Results from the analysis of each of the 10 imputed datasets will be combined using Rubin's imputation rules (Rubin 1987) to produce a pooled least squares mean (LSM) estimate of treatment difference.

MI analysis with Missing Not at Random (MNAR) assumption (placebo-based): A placebo-based multiple imputation will be performed using a pattern mixture model under the assumption of MNAR for each co-primary endpoints. For these analyses, the imputation model will be estimated using placebo subjects only. The imputation models will include the randomization stratification factor, the baseline value of the endpoint, and all previous values of the endpoint at each time point. See Ratitch and O'Kelly (2011) for additional details regarding the methodology used to obtain the placebo-based imputation datasets. Similar methods as described for the previous multiple imputation method will be used to produce a pooled LSM estimate of treatment difference.

Completers analysis: An Analysis of Covariance (ANCOVA) will be employed for Week 16 NPS for subjects who completed Week 16 only, where the change from baseline at Week 16 is modeled with baseline NPS score as covariate and treatment as a factor.

All primary and supplementary statistical analyses will be performed for the Full Analysis Set. If the Full Analysis Set and the Per Protocol Analysis Set differ by more than 10 subjects, the primary analysis of NPS will be repeated for the Per Protocol Analysis Set.

8.1.2. Sino-Nasal Outcome Test (SNOT-22)

The SNOT-22 is a 22-item outcome measure on a 5-category scale applicable to sino-nasal conditions and surgical treatments. For each item, the score ranges from 0 (No problem at all) to 5 (Problem as bad as it can be), and hence for the 22-items, the total score ranges from 0 to 110. Higher total scores on the SNOT-22 imply greater impact of CRS on QoL.

The SNOT-22 will be completed as indicated in the SoA (see Section 3.9) and is located on the clinical tablet. This frequent SNOT-22 might provide a kinetic profile of etokimab efficacy in subjects with CRSwNP.

For analysis purposes, baseline SNOT-22 score will be defined as the last value reported on or prior to the first dose date (Day 1). Total SNOT-22 values will also be obtained at each visit during Treatment Period (Week 4, 8, 12 and 16), and at the end of the Safety Follow-up Period (Week 24). A listing of SNOT-22 score and the change from baseline will be provided per visit per subject.

8.1.2.1. *Definition of Estimand*

The SNOT-22 is measured every 4 weeks during treatment and at end of treatment (Week 16). The primary time point is Week 16. A general linear MMRM using the change from baseline in SNOT-22 scores at Weeks 4, 8, 12, and 16 as response; baseline (Day 1) SNOT-22 score as fixed covariate; treatment group, randomization stratification factor, time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect; and subject as a random effect will be used to obtain least squares means to compare the etokimab treatment arms with the placebo arm.

Summary statistics for each time point will include n, mean, standard deviation, median, minimum, and maximum, for baseline, each time of measurement, and the change from baseline calculated as post baseline value minus the baseline value.

Subjects are also asked to choose the maximum of 5 most important items that are affecting their health at each SNOT-22 assessment. A summary table for each time point will be provided including the frequency and percentage of each item chosen as the top 5 items.

8.1.2.2. *Primary Statistical Analysis for SNOT-22*

The (co)primary hypothesis to be tested for this estimand is that treatment of adults diagnosed with CRSwNP using etokimab will result in a significantly greater reduction of Week 16 SNOT-22 from baseline when compared to placebo. This hypothesis will be tested by comparing the least squares adjusted means for each etokimab dose group with placebo, at the Week 16 time point. 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 dropouts are regarded as missing at random (MAR). The same procedure employed to NPS will be repeated for the primary statistical analysis of SNOT-22.

Graphical displays of the results will be presented. The (by time-point) least squares means and two-sided 95% confidence intervals for each treatment depicted with error bars will be plotted against time, and the p-values for the Week 16 comparisons will be displayed on the Week 16 time point.

8.1.2.3. *Supplementary Statistical Analysis for SNOT-22*

In order to assess the impact of missing data due to dropouts, sensitivity analyses will be performed where their data after dropout will be imputed using multiple imputation and the statistical analysis using MMRM will be repeated. The same supplementary analysis listed in section 8.1.1.3 will be performed for SNOT-22.

8.2. Secondary Efficacy Endpoint(s) and Analyses

Analysis of secondary efficacy endpoints will be performed in a hierarchical order to adjust for statistical multiplicity.

If the co-primary efficacy endpoints show statistical significance at the 2-sided significance level of 0.05, the secondary efficacy endpoints will be first tested at the significance level of 0.05 in the following order for the etokimab Q4W treatment arm versus placebo, then they will be tested at the significance level of 0.05 in the same order for the etokimab Q8W treatment arm versus placebo. During the hierarchical testing of the secondary endpoints, if the analysis of a particular secondary endpoint results in a p-value ≥ 0.05, the subsequent secondary endpoints will not be interpreted for statistical significance.

1. Time to first response (≥ 1 point improvement) in NPS
2. NPS response defined as a reduction of at least 1.0 from baseline to Week 16 in NPS
3. SNOT-22 response defined as a reduction of at least 12.0 from baseline to Week 16 in SNOT-22
4. Change from baseline to Week 16 in sense of smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT)

8.2.1. Time to First Response (≥1 Point Reduction in NPS)

Time to first response (≥1 point reduction in NPS), TTFR, is defined as the number of days from the first dose date to the date of a subject's first ≥1 point reduction in NPS, if a subject experiences a ≥1 point reduction in NPS. It will be calculated as:

TTFR = Date of first occurrence of ≥1 point reduction in NPS – date of first dose + 1

It is conceivable that a subject may achieve a ≥1 point reduction and lose it on the next visit. This endpoint only analyzes the time to the first response. Subjects who do not have an on-study occurrence of a ≥ 1 point reduction in NPS will have their TTFR censored at the last study evaluation time point in which NPS was collected. It will be calculated as:

TTFR = Last date of study evaluation of NPS – date of first dose + 1

The TTFR survivor functions will be estimated and plotted using the Kaplan-Meier method.

The logrank test stratified by the randomization factor will be performed for each etokimab dose regimen to evaluate whether it has a shorter time to first response than the Placebo group. The null hypothesis is that there is no treatment difference in the probability of achieving a ≥1 point reduction in NPS at any time during treatment; in other words, that the survivor functions for the time to ≥1 point reduction in NPS coincide. The alternative hypothesis is that the survivor functions are different.

A statistically significant shorter time to response (logrank test 2-sided p-value < 0.05) for the etokimab dose group when compared to the Placebo group will be taken as evidence in favor of efficacy of etokimab compared to placebo.

Summaries from the analysis will include a Kaplan-Meier plot of the survivor functions, a table summarizing the number of subjects in each treatment group, the number of events, the number censored, and the 25^{th} and 75^{th} percentile survival time estimate and median survival time estimate and their 95% CI, if estimable, and the p-value of the logrank test. A listing for each subject's time to first response will be provided.

The logrank test is based on the assumptions that the censoring mechanism is independent of the occurrence of an event (achieving ≥1 point reduction in NPS), the survival probabilities are the same for subjects recruited early and late in the study, and the events happened at the times specified. Events may not necessarily have occurred at the clinic visits, but they are ascertained at those visits. Since clinic visits are equally spaced and planned per protocol, we may regard this last assumption to be loosely satisfied. A more accurate assessment will require use of methods for handling interval censored data. In other words, since NPS is measured only at clinic visits, this endpoint may be interval censored: a subject's ≥1 point reduction could occur at time points between clinic visits but no NPS measurements are taken in between planned clinic visits. If deemed important and necessary, statistical methods appropriate for interval censored data may be explored and implemented.

8.2.2. Responder Analysis: Week 16 NPS Score Decrease of ≥1 from Baseline

One of the (co)primary endpoints is the change from baseline in NPS score at Week 16. For this variable, a responder may be defined as a subject whose NPS score at Week 16 decreased from baseline by at least 1.0. If

the subject did not make it to Week 16, or if the subject did not achieve an NPS score reduction ≥1, the subject will be deemed a "Non-responder" (Response='No').

Summary statistics for each treatment group will include the number (n) and percentage (%) of subjects who responded, and an exact confidence interval for the % responders.

A logistic regression will be employed with terms for treatment (3 levels: 1=Placebo, 2=Eto Q8W, 3=Eto Q4W), baseline as a continuous covariate, and stratification factor (asthma comorbidity:1=Yes, 0=No).

Using the logistic regression model, for each comparison of the etokimab groups with the Placebo group, the estimated odds ratio for the etokimab versus placebo odds of response, a 95% Confidence Interval for the odds ratio, and the p-value for that comparison will be displayed in the summary table.

It is expected that treatment with etokimab should lead to a greater odds of response vs. not responding, when compared to the Placebo group. A statistically significantly greater odds ratio for the etokimab vs. placebo group comparison will be taken as evidence of efficacy in favor of etokimab.

8.2.3. Responder Analysis: Week 16 SNOT-22 Score Decrease of ≥ 12 from Baseline

The second co-primary endpoint is the change from baseline in SNOT-22 score at Week 16. For this variable, a responder may be defined as a subject whose SNOT-22 score at Week 16 decreased from baseline by at least 12. This cutoff point is based on the minimal clinically important difference (MCID) value reported by Phillips et al. (2018) and Phillips et al. (2019). If the subject did not make it to Week 16, or if the subject did not achieve an SNOT-22 score reduction ≥ 12, the subject will be deemed a "Non-responder" (Response='No').

Summary statistics for each treatment group will include the number (n) and percentage (%) of subjects who responded, and an exact confidence interval for the % responders.

The same logistic regression as the responder analysis for NPS score will be employed for SNOT-22. It is expected that treatment with etokimab should lead to a greater odds of response vs. not responding, when compared to the Placebo group. A statistically significantly greater odds ratio for the etokimab vs. placebo group comparison will be taken as evidence of efficacy in favor of etokimab.

8.2.4. University of Pennsylvania Smell Identification Test (UPSIT)

The University of Pennsylvania Smell Identification Test (UPSIT) is a commercially available test used for smell identification to test the function of an individual's olfactory system. It can be self-administered and uses microencapsulated odorants which are released by scratching standardized odor-impregnated test booklets. This 40-item test will be self-administered by subjects at clinic visits on Day 1 (before injection), Week 8 (before injection) and Week 16/EOT. It usually takes 10-15 minutes.

The test consists of 4 different 10 page booklets, with a total of 40 questions. On each page, there is a different "scratch and sniff" strip which is embedded with a microencapsulated odorant. There is also a four choice multiple choice question on each page. The scents are released using a pencil. After each scent is released, the patient smells the level and detects the odor from the four choices. There is an answer column on the back of the test booklet, and the test is scored out of 40 items.

An UPSIT result is scored out of 40. A higher score indicates better olfaction, and scores of 35-40 indicate normal sense of smell (Doty et al.). A single numeric score is collected in CRF.

Summary statistics for each time point will include n, mean, standard deviation, median, minimum, and maximum, for baseline and the change from baseline.

Each etokimab dosing regimen will be compared to the Placebo group via a MMRM modeling the change from baseline in the UPSIT score at Week 16 as the dependent variable; baseline (Day 1) UPSIT score as a covariate, treatment group (3 levels), stratification factor, treatment by stratification factor, categorical time point (Weeks 4, 8, 12 and 16) and treatment by time interaction as fixed effect factors, and subject as a random effect in the model.

8.3. Exploratory Efficacy Endpoints

8.3.1. Patient Reported Quality of Life Scales

8.3.1.1. *Medical Outcomes Study 36-item Short Form (SF-36)*

The SF-36 is a generic health survey with 36 items (Ware et al. (1992); Hays et al. (1993)) that measure functional health and well-being from the subject's perspective and will be assessed during clinic visits on Day 1 and Weeks 4, 8, 12, 16 and 24. The 36 questions are grouped into 11 sections of questions in the questionnaire. Some of the sections consist of multiple questions. The 36-item patient-reported questionnaire covers eight health domains: physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items).

To specify scoring formulas, the 11 sections of the SF-36 are denoted by Q1 to Q11 according to the order in the questionnaire and the individual items in each question are denoted by their alphabetic order. These may be restated into items 1 to 36 (Please refer to Appendix 19.1).

Scores for each domain range from 0 to 100, with a higher score defining a more favorable health state. The 8 scaled scores are weighted sums of the questions in each section. Scores range from 0 – 100, with lower scores indicating more disability and higher scores indicating less disability. The 8 dimensions/scales are: Physical functioning (PF), Role limitations due to physical health (RP), Role limitations due to emotional problems (RE), Energy/Fatigue (or, Vitality) (VT), Emotional Well-being (or, Mental Health) (MH), Social functioning (SF), Pain (BP), and General Health (GH).

From the eight health dimensions, a physical component summary (PCS), which is the aggregate score of the PF; RP; BP and GH scales, and mental component summary (MCS) which is the aggregate score of the VT; SF; RE and MH scales, measures may be derived. No total score will be derived. (Lins L. et al. (2016)).

Summary statistics for each of the 8 domains and for the PCS and MCS for Day 1, and Weeks 4, 8, 12, 16, and 24 will include n, mean, standard deviation, median, minimum and maximum for baseline, the time of measurement, and the change from baseline.

For the PCS and MCS separately, the change from baseline at Weeks 4, 8, 12 and 16 will be modeled using an MMRM with baseline SF-36 as covariate, treatment group (3 levels), stratification factor, treatment by stratification factor, categorical time point (Weeks 4, 8, 12 and 16) and treatment by time interaction as fixed effect factors, and subject as a random effect. Treatment comparisons will be based on the week 16 least squares means and standard errors. Associated 95% confidence limits for the LS means and the p-value for comparison of each etokimab dose group with the Placebo group will be displayed.

8.3.1.2. *European Quality of Life Scale (EQ-5D)*

The impact of CRSwNP on the quality of life of the patient will be assessed using the EQ-5D questionnaire. This questionnaire has two components: health state description and evaluation.

In the description part, the EQ-5D-5L health questionnaire is a health-related quality of life instrument with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 possible levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

The summary of results will follow the EQ-5D-5L guidelines for results presentation. For the "Health Profiles" descriptive system summary results will show the number, and proportion (%) of subjects in each Item score (No Problems, Slight Problems, Moderate Problems, Severe Problems, Extreme Problems) by treatment at baseline and at each visit (Weeks 4, 8, 12, and 16).

No formal statistical testing will be carried out for the EQ-5D-5L.

In the evaluation part, the EQ-VAS measures overall self-rated health status on a 0-100 scale, with 0=worst health you can imagine and 100=best health you can imagine. Thus higher scores are suggestive of better health status.

Summary statistics will be presented for the EQ-VAS score showing number of subjects, mean, standard deviation, median, minimum and maximum for each treatment group at baseline and each visit (Weeks 4, 8, 12 and 16), and change from baseline.

An MMRM with the baseline EQ-VAS score as covariate, and treatment (3 levels), stratification factor, treatment by stratification factor, categorical time point (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors, and subject as a random effect will be used to obtain least squares estimates for the change from baseline in EQ-5D VAS score in Week 16 for each treatment group. Each etokimab dose group will be compared to the Placebo group using the Week 16 least squares means and standard errors obtained from the model. Associated 95% confidence limits for the LS means and p-values for the treatment comparisons will be displayed.

8.3.1.3. *Patient Related Rhinosinusitis Severity Using Visual Analog Scale (VAS)*

The Visual Analogue Scale (VAS) for rhinosinusitis is used to evaluate the total severity. The patient is asked to indicate on a continuous scale (VAS) the answer to the question: "How troublesome are your symptoms of rhinosinusitis?" The VAS score ranges from 0 (Not troublesome) to 10 (Worst thinkable troublesome).

The disease severity can be divided into MILD, MODERATE and SEVERE based on total severity visual analogue scale (VAS) score (0 to 10 cm):

- MILD = VAS 0-3
- MODERATE = VAS >3-7
- SEVERE = VAS >7-10

The VAS is administered weekly via an electronic diary device. On Day 1, the eDiary is presented to the subject prior to dosing and the subject must complete the VAS scale before receiving study drug.

The value obtained on Day 1 is the subject's baseline value.

Summary statistics for the VAS for Day 1 and the following weeks until Week 24 will include n, mean, standard deviation, median, minimum and maximum for baseline, the time of measurement, and the change from baseline.

Statistical analysis for the change from baseline in VAS scores at Weeks 4, 8, 12, and 16 will be modeled using an MMRM with baseline VAS score as covariate, and treatment (3 levels), stratification factor, treatment by stratification factor, categorical time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors, and subject as a random effect included in the model. Treatment comparisons will be based on the Week 16 least squares means and standard errors. Associated 95% confidence limits for the LS means and the p-value for comparison of each etokimab dose group with the Placebo group will be displayed.

8.3.1.4. *Number of Nocturnal Awakenings*

Daily from Day 1 throughout the study, subjects recorded the number of their nocturnal awakenings on the eDiary. Subjects were asked "How many times did you wake up last night." The value obtained on Day 1 will be the subject's baseline value. All other values will be mapped into the weekly analysis visits specified in Section 6.4. Average daily value per each analysis week will be calculated for analysis. Only subjects with a value recorded more than 4 days per week will be included in the analysis.

Summary statistics including mean, standard deviation, median, minimum and maximum at each time point will be provided.

8.3.2. Lund-Mackay Scores

Computed tomography of the sinuses is performed at the clinic on Day 1 and at EOT (Week 16). The Day 1 CT is collected prior to dosing on Day 1. As indicated in the protocol, 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 that the subject is likely eligible for the study. CTs collected within 3 months prior to randomization (Day 1) can be used in lieu of a new Day 1 CT if the necessary imaging requirements are present.

The Lund-Mackay (L-M) scoring 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, and 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). 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). An aplastic

(absent) frontal sinus receives a score of 0. Thus, a combined L-M score of up to 24 is possible. The table below summarizes the scoring system:

Sinus	Right sinus	Left sinus
Frontal	0, 1, 2	0, 1, 2
Anterior ethmoids	0, 1, 2	0, 1, 2
Posterior ethmoids	0, 1, 2	0, 1, 2
Maxillary	0, 1, 2	0, 1, 2
Sphenoid	0, 1, 2	0, 1, 2
Ostiomeatal complex	0, 2	0, 2
Total score for each side	0-12	0-12

For the sinuses: 0=normal; 1=partial opacification; 2=total opacification.
For the ostiomeatal complex: 0=not occluded; 2=occluded

The L-M total score is obtained by summing the scores for the right and left sinuses. For simplicity, we will refer to the total score as the L-M score. Higher values for the L-M scores indicate more opacification.

Baseline L-M score will be defined as the L-M score obtained on Day 1, or the last available L-M score prior to treatment on Day 1. The L-M score at Week 16/EOT will be defined as the last value available during the treatment period.

Summary statistics will include n, mean, standard deviation, median, minimum, and maximum, and the percent change from baseline. A Wilcoxon signed ranks test p-value for the within treatment group percent change from baseline will be displayed.

Each etokimab dosing regimen will be compared to the Placebo group via an analysis of covariance (ANCOVA) modeling the percent change from baseline in L-M score at Week 16/EOT using the baseline L-M score as a covariate, with treatment (3 levels) as a factor. Least squares adjusted means from the ANCOVA model will be used to perform pairwise comparisons of each etokimab dosing regimen with the Placebo group. An estimate of treatment difference and accompanying 95% confidence intervals will be produced from the model. Each (two-sided) comparison of an etokimab dose group with the Placebo group with respect to L-M scores will use the 5% level of significance.

8.3.3. Nasal Peak Inspiratory Flow (NPIF) (AM and PM)

Nasal Peak Inspiratory Flow (NPIF) will be used to evaluate nasal flow through the nose. At screening (Visit 1), subjects will be issued an NPIF meter for recording morning (AM) and evening (PM) NPIF. Subjects will record values (L/min) twice a day for 7 consecutive days during screening period, and twice a day, every day throughout the treatment and safety follow-up period (Week 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 MFNS

Three NPIF efforts will be made by the subject and recorded. 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 (PM) NPIF will be the mean AM (PM) measurement recorded for 7 consecutive days or 1 week during the screening period, prior to the first dose of investigational product. 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.

During the screening period NPIF recordings are collected on paper diary provided to subjects. Starting from Day 1, subjects are provided an eDiary to collect NPIF recordings throughout the remainder of the trial. Diary compliance must be approximately 80% throughout the study duration. For both the paper diary utilized during the screening period and the eDiary during the treatment period,the NPIF meter is set up only to allow for a value equal to or greater than 30, so the lowest NPIF value a subject can record is set at 30.

NPIF (AM and PM) means will be calculated for each week only for the subjects who have greater than 50% of diary compliance for that specific week:

Summary statistics for each month will include n, mean, standard deviation, median, minimum and maximum, and the change from baseline. For each treatment arm, a Wilcoxon signed ranks test will be used to assess whether the change from baseline is statistically significant.

The etokimab dose groups will be compared to the Placebo group during the treatment period (up to Week 16) only. The values obtained between Week 17 and Week 24will not be included in the efficacy analysis, as follow-up is intended for safety only.

Statistical analysis of morning/evening NPIF during the treatment period will employ an MMRM, where the change from baseline in Weeks 4, 8, 12 and 16 AM (PM) NPIF values are modeled using the baseline value as a covariate; treatment (3 levels), stratification factor, treatment by stratification factor, categorical time (Weeks 4, 8, 12 and 16), and treatment by time interaction as fixed effect factors; and subject (the repeated measures) as random effect. The analysis is similar to that performed for the NPS and SNOT-22 scores.

The primary time point for the analysis of morning/evening NPIF is Week 16. The Week 16 least squares adjusted means from the MMRM will be used to perform pairwise comparisons of each etokimab dosing regimen with the Placebo group. An estimate of treatment difference and accompanying 95% confidence intervals will be produced from the model. It is expected that treatment with etokimab will lead to higher AM/PM NPIF values at Week 16 than obtained at baseline. A statistically significant difference ($P<0.05$) where the least squares means for the etokimab group is higher than for the Placebo group will be regarded as evidence of efficacy for etokimab compared to Placebo.

8.3.4. Subgroup Analysis in Subjects with Comorbid Asthma

Statistical analyses will be carried out for subjects who have comorbid asthma.

8.3.4.1. *Asthma Subjects: NPS*

The primary endpoint analysis of NPS will be repeated among subjects with comorbid asthma.

As was done for the primary endpoint, summary statistics will be provided for the subgroup of subjects with comorbid asthma, for baseline, each time of measurement, and for changes from baseline.

For subjects with comorbid asthma only, statistical analysis of NPS will employ an MMRM where the change from baseline in NPS at Weeks 4, 8, 12 and 16 values are modeled using the baseline (Day 1) value as a covariate; treatment (3 levels), time (Weeks 4, 8, 12 and 16), and treatment by time interaction as fixed effect factors; and subject (the repeated measures) as random effect in the model.

8.3.4.2. *Asthma Subjects: SNOT-22*

The primary endpoint analysis of SNOT-22 will be repeated among subjects with comorbid asthma. The same summary statistics and analyses described in 8.3.4.1 for NPS will be repeated for SNOT-22.

8.3.5. Change in the Percentage of Volumetric Maxillary Sinus Occupied by Disease (VMSOD)

At clinic visits on Day 1 and Week 16/EOT, computed tomography (CT) scans are used to calculate the volume of the air (mL), the volume of the mucosa (mL), the % occupied by disease, and the thickness of the lateral wall. Central reading before Day 1 (Visit 2) will be used for comparison with the 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 percentage occupied by disease will be analyzed. Baseline is defined as the percentage of VMSODs on Day 1. The Week 16/EOT value is the % of VMSOD at the Week 16/EOT assessment. For each subject, the difference in the % VMSOD between the Week 16/EOT and baseline values will be calculated (EOT value minus baseline value) as a measure for the percent change in opacification.

Summary statistics for % of VMSOD for baseline value, Week 16/EOT value, and the change from baseline (Week 16/EOT minus baseline) will include n, mean, standard deviation, median, minimum, and maximum. For each treatment arm, a Wilcoxon signed ranks test will be used to assess whether the change from baseline is statistically significant.

Statistical analysis of the change in % VMSOD from baseline at Week 16/EOT will be performed using ANCOVA with baseline % VMSOD as a continuous covariate, and treatment (3 levels) as a factor. Gender (M/F) may be considered for inclusion in the model. If preliminary analysis shows the gender-by-treatment interaction term to be not significant at alpha=0.05, the gender-by-treatment term will be dropped out of the model. The final model may include main effect for gender if this is deemed important to adjust for.

Least squares adjusted means from the final ANCOVA model will be used to perform pairwise comparisons of each etokimab dosing regimen with the Placebo group. An estimate of treatment difference and accompanying 95% confidence intervals will be produced from the model.

Each (two-sided) comparison of an etokimab dose group with the Placebo group with respect to % VMSOD will use the 5% level of significance. It is expected that treatment with etokimab will lead to lower % VMSOD values at week 16/EOT than observed at baseline. A statistically significantly higher adjusted mean score for an etokimab group compared to the Placebo group will be regarded as evidence of efficacy for etokimab compared to Placebo.

8.3.6. FEV_1 and % Predicted FEV_1

FEV_1 (L/min) will be obtained by spirometry at each clinic visit during the treatment period (on Day 1, Week 4, 8, 12, and 16). The FEV_1 value will be recorded in the CRF. FEV_1 and % Predicted FEV_1will be analyzed for all subjects, as well as among subjects with comorbid asthma.

Summary statistics will be provided for all subjects, as well as for the subgroup of subjects with comorbid asthma, for baseline, each time of measurement, and for changes from baseline.

For all subjects, and again for subjects with comorbid asthma only, statistical analysis of FEV_1 and % Predicted FEV_1 will employ an MMRM where the changes from baseline at Weeks 4, 8, 12 and 16 values are modeled using the baseline (Day 1) value as a covariate; treatment (3 levels), stratification factor (for all subjects model only), treatment by stratification factor (for all subjects model only), time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors; and subject (the repeated measures) as random effect.

Treatment comparisons between etokimab and Placebo groups will use the Week 16 least squares means and associated standard errors. Ninety-five percent confidence intervals will be obtained for both parameters, and p-values for comparison of etokimab with placebo groups will be presented.

8.3.7. ACQ-7

The Asthma Control Questionnaire, ACQ-7, is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ-7 has 7 items with 1 week clinic recall for items on symptoms and rescue inhaler use. Subjects are asked to recall their experiences during the previous week by responding to 5 symptoms related questions and 1 question related to bronchodilator use and clinic staff complete 1 question on FEV_1%. As part of compliance measure, subjects are required to answer to all of the first 6 questions (eg., symptoms related and bronchodilator use).

It 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.

The items are answered on a 7-point scale (0=totally controlled, 6=severely uncontrolled; and 7 categories for FEV_1%).

ACQ-7 total score calculated as the mean of the responses to all 7 questions.

ACQ-7 is administered at clinic visits on Day 1, and at Weeks 4, 8, 12 and 16. Baseline ACQ-7 total score is the mean score on Day 1. The ACQ-7 mean score will be calculated for each clinic visit.

Summary statistics for the ACQ-7 score for baseline, each time of measurement, and changes from baseline, will be obtained for each treatment group. A Wilcoxon signed ranks test p-value will be obtained for the within treatment group change from baseline.

The ACQ-7 at Week 16 will be compared between etokimab and placebo groups using an MMRM with change from baseline at Weeks 4, 8, 12, and 16 as response, baseline ACQ-7 total score as a covariate, treatment (3

levels), time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors; and subject as a random effect.

Least squares means for each time of measurement and associated standard errors and 95% confidence intervals will be provided, as well as the p-values for comparing the Week 16 least squares means between each etokimab dose group and the placebo group.

8.3.7.1. *ACQ-5*

While subjects are expected to respond to all 6 questions (5 symptom related and 1 bronchodilator use items), FEV1 may be still missing if a subject was not able to complete the spirometry test. As a supplementary analysis, the same analyses described in Section 8.3.7 will be repeated on ACQ-5, which is only based on the first 5 symptoms related questions. ACQ-5 total will be calculated in the same way as ACQ-7 and the average of the 5 items will be used for analysis.

8.3.8. Blood Eosinophil Count from Baseline to Week 16

Blood eosinophil count (EOS) is a marker of asthma exacerbation risk, and evidence suggests that reducing EOS leads to improved outcomes in severe asthma. Blood samples for laboratory tests (including eosinophil tests) are collected at each clinic visit.

Summary statistics for eosinophil blood count (absolute) will be provided using n, mean, standard deviation, median, minimum, and maximum at baseline and at Weeks 4, 8, 12, and 16/EOT. Additionally, the within treatment group changes from baseline will be assessed for significance from 0 using a Wilcoxon signed ranks test; the p-value will be presented.

An MMRM will be used to compare each of the etokimab treatment groups with the placebo group with respect to the change from baseline in absolute eosinophil count at Week 16/EOT using the baseline as a covariate, treatment (3 levels), stratification factor, treatment by stratification factor, time (Weeks 4, 8, 12, and 16), and treatment by time interaction as fixed effect factors; and subject (the repeated measures) as random effect.. Treatment comparisons between etokimab and Placebo groups will use the Week 16 least squares means and associated standard errors. Ninety-five percent confidence intervals will be obtained for both parameters, and p-values for comparison of etokimab with placebo groups will be presented.

8.3.9. Time to Treatment Discontinuation

Time to treatment discontinuation will be calculated as the number of days from the randomization date to the date the subject discontinued study medication. This variable is censored for subjects who did not discontinue study medication and completed the treatment. The censoring date is the date of treatment completion.

The time to discontinuation will be analyzed using methods for survival data. Kaplan-Meier plots of the estimate of survivor function for the 3 treatment arms will be provided in one graph. A log-rank test will be used to compare each etokimab dose group with the Placebo group.

8.3.10. Incidence of Treatment Discontinuation Due to Oral Corticosteroids or Nasal Polyp Surgery

Use of rescue medication (e.g., 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.

The incidence of treatment discontinuation due to oral corticosteroids or nasal polyp surgery will be summarized in a table showing the number and % of subjects in each group. Comparisons of each etokimab dose group with the Placebo group will be based on a Fisher's exact test.

8.3.11. Change in Nasal Polyp Related Resource Use Questionnaire from Baseline to Week 16

The Nasal Polyp Related Resource Use Questionnaire is a questionnaire of health care resource utilization for nasal polyposis (e.g., specialist visits, emergency care visits, sick leaves, days off) and will be completed as indicated in Table 1.

Outpatient specialist visits will be summarized by visit with number and % of subjects responding. Days missed from work and Days missed from usual activities due to nasal polyp will be summarized with the number of respondents, the mean and standard deviation, median, minimum and maximum.

Change in nasal polyp related resource use from baseline may be evaluated for days missed from work/usual activities due to nasal polyps using the MMRM specified in Section 8.3.8. No formal statistical inference is planned for the rest of the items from this questionnaire.

9. ANALYSIS OF PHARMACOKINETICS

Blood sample for pharmacokinetic analysis will be obtained according to the schedule indicated in Section 9.1. The PK Analysis Set will be used to create subject listings of all concentration-time data following study drug administration and will be presented by subject and actual sample collection time. The PK Analysis Set will be used to list and summarize serum etokimab concentrations for each sampling time point using appropriate descriptive statistics by cohort and nominal study day.

9.1. PK Sampling Schedule

Blood sample for pharmacokinetic analysis will be obtained at each clinic visit according to the schedule in the table below.

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. PK can be pulled at any time during the study visit	
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	Anytime 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

9.2. Serum PK Endpoints

The PK endpoints for this study will be listed in a separate PK SAP and analysed by AnaptysBio, Inc PK team.

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data

- Missing PK concentrations will not be imputed, except that if the Day 1 pre-dose concentration is missing then a value of zero will be used.
- If the collection time of a sample is not recorded, then the nominal time will be used to determine PK parameters.

9.3.2. Listing and Presentation of Individual PK Data

- Individual concentration-time data will be listed and plotted by actual sampling times on linear and semi-logarithmic scales.

- Patient listings of PK sampling dates and times and all concentration-time data for each treatment will be presented.

- Graphs for mean concentration-time data following SC administration will be presented by their respective treatment groups. Plots of the mean (±SD) serum concentration-time profile for etokimab by cohort will be presented by nominal sampling time on linear and semi-logarithmic scales.

- Concentration-time data may be summarized by ADA status (confirmed ADA positive versus those without positive ADA response; patients with neutralizing ADAs).

9.3.3. Summary of PK Concentrations

- Mean serum concentrations will be summarized by treatment using descriptive statistics.

- PK concentrations will be summarized by treatment group and nominal time point using n, mean, SD, coefficient of variation (CV), minimum, median, and maximum. For PK concentrations, the number of observations ≥ lower limit of quantitation (LLOQ) will also be included.

- Pharmacokinetic concentration will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry.

10. SAFETY

Safety will be assessed from adverse event (AE) reports, clinical laboratory data, ECG data, physical examination test results, and vital sign parameters. The population used for safety analyses will be the Safety Analysis Set (SS).

All safety analyses will be reported by treatment group as well as combined for the 16-week treatment period unless noted otherwise.

10.1. Extent of Exposure

Etokimab is administered subcutaneously. The predicted etokimab half-life is approximately 14 days. The PK data generated to date indicate that a linear PK profile is observed upon etokimab administration regardless of the route. Hence, for the sake of calculating duration of treatment exposure in this study, we will assume that a subject's exposure to study medication continues up to 28 days after SC injection. Thus, duration of total exposure will be calculated per subject as follows:

Duration of total exposure = (Date of last dose of study medication + 28) – Date of first dose of study medication + 1

Duration of total exposure and total drug administered will be summarized by treatment group for the Safety Analysis Set using n, mean, standard deviation, minimum, Q_1, median, Q_3 and maximum. Study drug administration per visit will be listed for the SAF.

10.2. Adverse Events

For the purpose of this study, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) that emerges or worsens following initial administration of the study medication (eg., mometasone furoate nasal spray) and until the end of study participation. The untoward medical occurrence may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant 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 serious adverse event (SAE) is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires hospitalization or causes prolongation of existing hospitalization.

A treatment-emergent AE (TEAE) is an AE that occurs or worsens in severity after any exposure to the investigational product (etokimab or placebo). If an AE starts between the screening visit and the randomization visit, and is ongoing at the time of treatment initiation, it may be deemed treatment emergent if it worsens in severity/severity. In that case, a separate event is to be recorded in the subject's eCRF indicating the worsened severity.

Section 6.3.4 of this SAP provides conventions for handling missing dates for AEs, for determining treatment emergence in the presence of missing data, and for assigning severity and treatment-relatedness in the presence of partial or missing start/stop AE dates.

All adverse events will be coded using MedDRA version 21.0 or higher. The TEAE reporting period begins with administration of the first dose of study medication on Day 1 and continues until the Visit 7 (Week 16 visit, or 28 days after the last dose of study medication). The Safety Follow-Up AE reporting period begins 29 after the last dose of study medication through completion of the Safety Follow-Up Period (Week 24 visit).

AEs are assessed with respect to relatedness by the investigator, as unrelated, possibly related, related, and definitely related. An AE would be categorized in statistical presentations as "treatment-related" if it is assessed by the investigator as possibly related, related, or definitely related. Any missing relationship will be categorized as "related" for the purpose of summarization.

The severity of AEs (whether nonserious or serious AEs) will be assessed by the investigator as follows:

- **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.

An AE with missing severity will be categorized as "severe" for purposes of summarization.

10.2.1. Tabulation of Adverse Event Data

The following tables will be produced to summarize AE data. For the following tables, subjects will be counted only once at each level of summarization.

- An overall summary of the number and percentage of subjects reporting TEAEs, TEAE severity, serious TEAEs, treatment-related TEAEs, related serious TEAs, TEAEs leading to interruption of study drug, TEAEs leading to permanent withdrawal of study drug; related TEAEs leading to permanent withdrawal of study drug, and TEAEs leading to death.

Summary tables by treatment group of the number of subjects (and percentage) with TEAEs as follows:

- TEAEs overall and by system organ class and preferred term
- Most common TEAEs (>=5% in any treatment group) by preferred term
- TEAEs by maximum severity, overall and by system organ class and preferred term
- Treatment-related TEAEs overall and by system organ class and preferred term
- Serious TEAEs, overall and by system organ class and preferred term
- Serious, treatment-related TEAEs overall and by system organ class and preferred term

- TEAEs leading to permanent withdrawal of study medication, overall and by system organ class and preferred term

Additional TEAE summaries will be provided by treatment group, including the number and percentage of subjects experiencing TEAEs for the following:

- TEAEs overall and by SOC and PT, including the following subgroup analyses:
    - Asthma comorbidity

These summaries will be prepared for TEAEs occurring during the treatment period. Similar summaries as above will be provided for AEs starting during the Safety Follow-up Period with the exception of AEs leading to permanent withdrawal of study medication and the subgroup analyses, which will be provided for the TEAEs only. Denominators for the Safety Follow-Up Period AE summaries will be based on the number of subjects entering the Safety Follow-Up Period.

In addition to the listing of all AEs, separate listings will be provided of serious AEs, AEs leading to permanent withdrawal of study medication, and AEs leading to death. TEAEs will be identified on each listing.

10.3. Laboratory Evaluations

Laboratory safety parameters will be analyzed by a central laboratory using standard validated methods. All laboratory safety data will be collected as per the schedule of assessments given in Table 1.

The following laboratory parameters will be collected:

- Hematology: hemoglobin, hematocrit, mean cell hemoglobin, mean cell volume, mean cell hemoglobin concentration, platelet count, red blood cell count, white blood cell with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Blood Biochemistry: alanine aminotransferase (ALT; SGPT), albumin (ALB), alkaline phosphatase (AP), aspartate aminotransferase (AST; SGOT), bicarbonate, bilirubin (total), bilirubin (direct), blood urea nitrogen (BUN), calcium (Ca), chloride (Cl), creatinine, creatine kinase, C-reactive protein, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), phosphate (inorganic), potassium (K), sodium (Na), total cholesterol (?fractions), total protein, triglycerides, troponin-I, uric acid.
- Urinalysis: bilirubin, blood (occult), glucose, ketones, leukocytes esterase, nitrites, pH, protein, specific gravity, urobilinogen.
- Follicle stimulating hormone: Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH)
- Immunoglobulin: Immunoglobulin E
- Viral Serology: hepatitis B surface antigen, hepatitis B and C antibody, HIV 1 and 2 antibodies
- Pregnancy tests: serum pregnancy test (human chronic gonadotropin), urine pregnancy dipstick
- Urine drug screens: amphetamine; barbiturates; benzodiazepines; cocaine; ethanol; marijuana; 3,4-Methylenedioxymethamphetamine (MDMA; ecstasy); methadone; methamphetamine; opiate; oxycodone; phencyclidine; TCA

- Tuberculosis B (TB) test: purified protein derivative (PPD) skin test, QuantiFERON® TB Gold (QFT)

Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings.

Observed continuous laboratory data will be descriptively summarized by type of laboratory test/parameter by treatment group. Changes from baseline will also be presented for all continuous laboratory parameters by treatment group over time. Shift tables using categories of low, normal, and high, comparing laboratory test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

All laboratory values (including values, reference ranges, and possible flags (low, high)) will be presented in the subject data listings

Line plots for neutrophils and leukocytes will be produced by plotting actual values against the sample collection time point for individual subjects.

10.4. Vital Signs

Vitals signs including weight are obtained according to the schedule in Table 1. Vital signs assessments should be performed before blood sampling and before injection of study medication at each study visit where administered. Blood pressure readings should be obtained after approximately 15 minutes of rest in a seated position. Vital signs captured include body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by treatment group and visit for Safety Analysis Set. The following conversion factor will be used to convert any temperatures reported in degrees Fahrenheit to Celsius:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

All vital signs values will be presented in the subject data listings.

10.5. ECG

At the screening, Day 1, Week 16/EOT and Week 24/EOS/ET visits, 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. For the analysis, the last measurement for the same visit will be included in the summary. If multiple measurements have the same date and time, the one recorded in the CRF will be evaluated for the summary table. 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.

Descriptive summaries of observed and change from Baseline values will be presented for each quantitative ECG parameter by treatment group and visit, including HR, PR, QRS, QT, QTcF, and RR.

ECG shift tables will be presented providing the count of subjects with each type of finding (normal, abnormal – NCS, or abnormal – CS) at Baseline compared to each post-baseline visit by treatment group with percentages based on subjects with a non-missing value at the Baseline and post-baseline visit.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges: > 450 for male or > 470 for female; > 500 for the post-baseline visits. Summaries of the number and percentage of subjects per visit and overall post-baseline visit will be provided for each of these ranges.

The changes in QTcF values will be categorized into the clinical concern ranges, which are specific to changes in QTcF: 30-60 and >60 msec. A summary of change in QTcF value will display the number and percentage of subjects with a change within each range per each visit. Subjects with missing baseline values will be excluded from this summary. All ECG parameters including the finding will be listed.

10.6. 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 post-treatment 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 post-treatment; significant findings that are present prior to investigational product administration are included on the Medical History page.

Physical examination results will be provided in a listing only.

10.7. Other Safety

10.7.1. Pregnancy Tests

Pregnancy test results will be provided in a listing only.

10.7.2. Immunogenicity Analysis

Blood samples will be taken for ADA analysis at pre-dose, week 4, 8, 12, 16, 20, and 24 (EOS).

A subject will be considered to be positive for etokimab-induced immunogenicity if one of the following criteria is met:

1. A missing pre-dose immunogenicity assessment and a confirmed positive immunogenicity response after dosing.

2. A negative pre-dose immunogenicity assessment and a confirmed positive immunogenicity response after dosing.

3. A positive pre-dose immunogenicity assessment and a confirmed positive immunogenicity response after dosing.

Observed values for ADA levels/status and the neutralizing antibody levels/status will be listed by subject and summarized with descriptive statistics based on the Safety Analysis Set. The frequency and percentage of confirmed positive immunogenicity response will be summarized by treatment groups. If data permits, correlation will be assessed between ADA levels and safety and efficacy endpoints.

Titer values will be summarized by treatment using mean and median. The frequency and percentage of patients with categorical result assessments will be summarized by treatment groups at each available visit and time point.

11. INTERIM ANALYSES

11.1. Independent Data Safety Monitoring Board or Data Monitoring Committee

A DSMB will be set up to review accumulating data. No formal statistical inference is planned for the accumulating safety data. However, the DSMB may recommend that the study be stopped if they assess that study subjects are being harmed by the investigational drug.

The first DSMB meeting occurred in May 2019. Subsequent DSMBs will be as per the DSMB charter.

11.2. Planned Formal Interim Analysis to Assess Efficacy and Safety

An interim analysis of co-primary efficacy endpoint 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 and determine the likelihood for further etokimab clinical development in other indications.

No adjustments to the current protocol are planned as a result of the interim analysis. Therefore, overall alpha is expected to be maintained at approximately 0.05, two-sided, for the co-primary efficacy endpoints. In addition to Week 8 analysis of the co-primary endpoints, the following will also be reviewed at the time of the interim:

- Disposition and analysis population
- Select baseline characteristics
- Spirometry values and change from baseline in spirometry by parameter and time point
- ACQ values and change from baseline by time point
- Eosinophil values and change from baseline by time point
- Treatment-emergent adverse events

Disposition and analysis population will be reported for Enrolled Set. Baseline characteristics and efficacy endpoints will be summarized for the FAS and by randomization stratification subset group (ie, asthma and non-asthma diagnosis). Longitudinal summaries will be presented up through the Week 8 time point. All adverse events reported up to the time of the interim analysis data cut will be included in the summaries of treatment emergent adverse events and reported for the Safety Analysis Set by actual treatment group assignment.

An unblinded team from [redacted]biostatistics will perform the analyses as described in Section 3.7 of this SAP (refer to blindin[redacted]tain the blinding of the study). The unblinded IA results will be made available only to the designated AnaptysBio personnel (employees and/or consultants) without direct contact with the sites.

12. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

In the protocol V4.0 Amendment 3 dated on 06Feb2020 version, analyses of nocturnal awakenings were defined to employ a Cochran-Mantel-Haenszen test (CMH) by visit using the data from the first item in ACQ-7. This original plan was later changed by AnaptysBio, Inc. to use the diary data instead.

The diary data are collected everyday from Day 1. AnaptysBio, Inc and [redacted] agreed that the diary data do not provide an appropriate baseline value as the data were collected on a single day, while the post-baseline values are derived from a weekly average, and decided to report descriptive statistics only for nocturnal awakenings. For this reason, the SAP Section 8.3.1.4 only specifies the summary statistics of nocturnal awakings and no description of statistical modeling is provided for the comparison of treatment groups to placebo.

13. REFERENCE LIST

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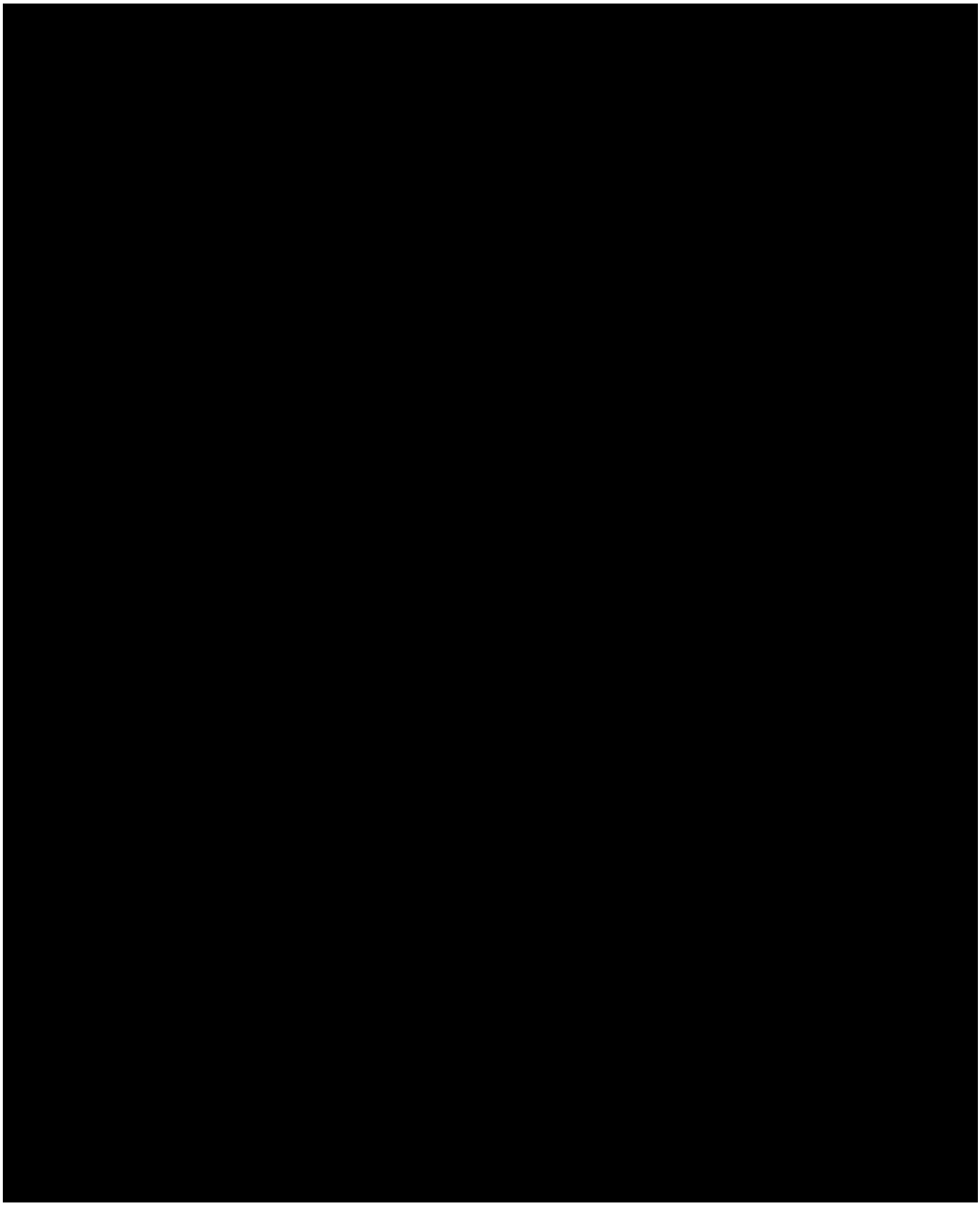
14. PROGRAMMING CONSIDERATIONS

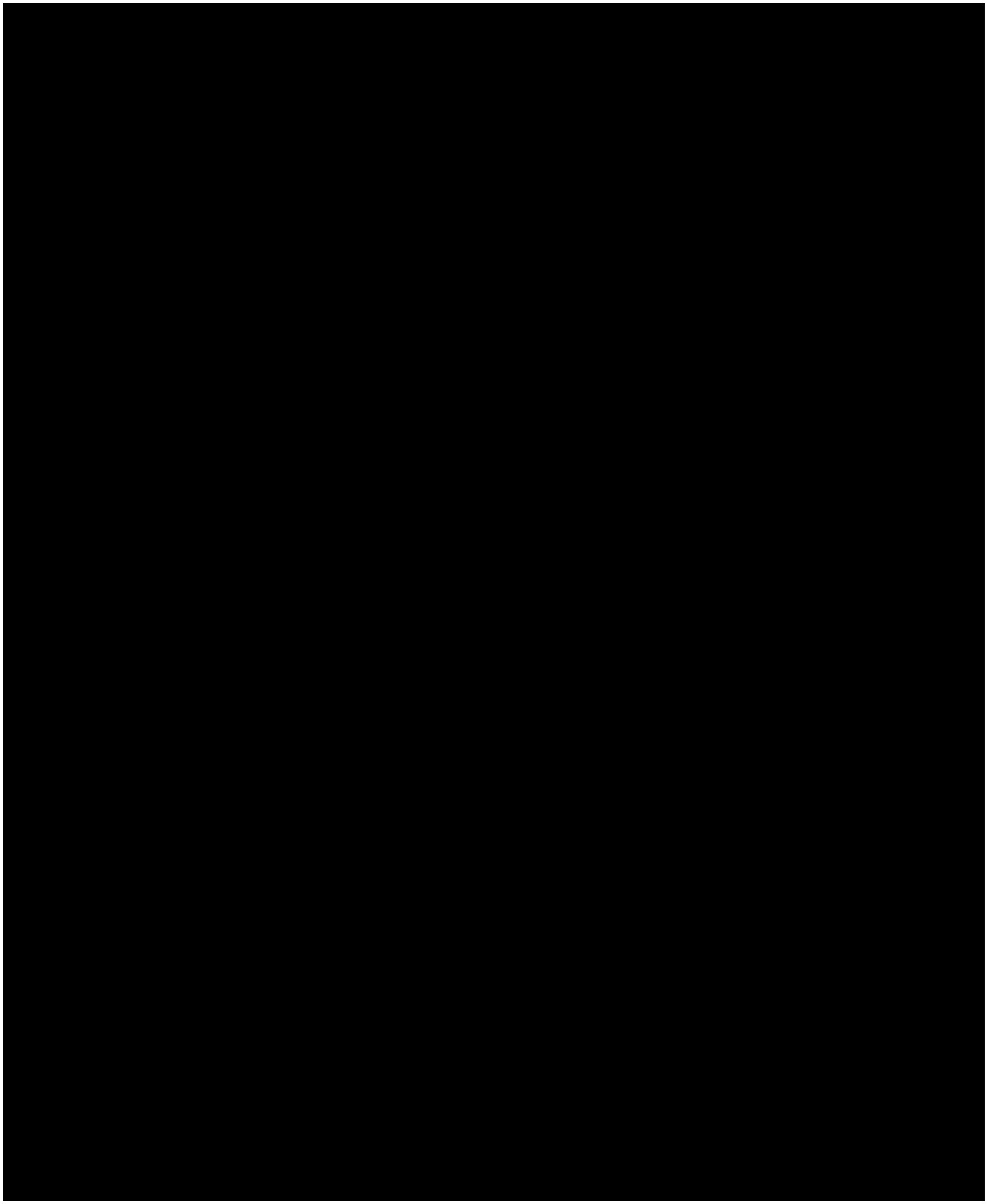
All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

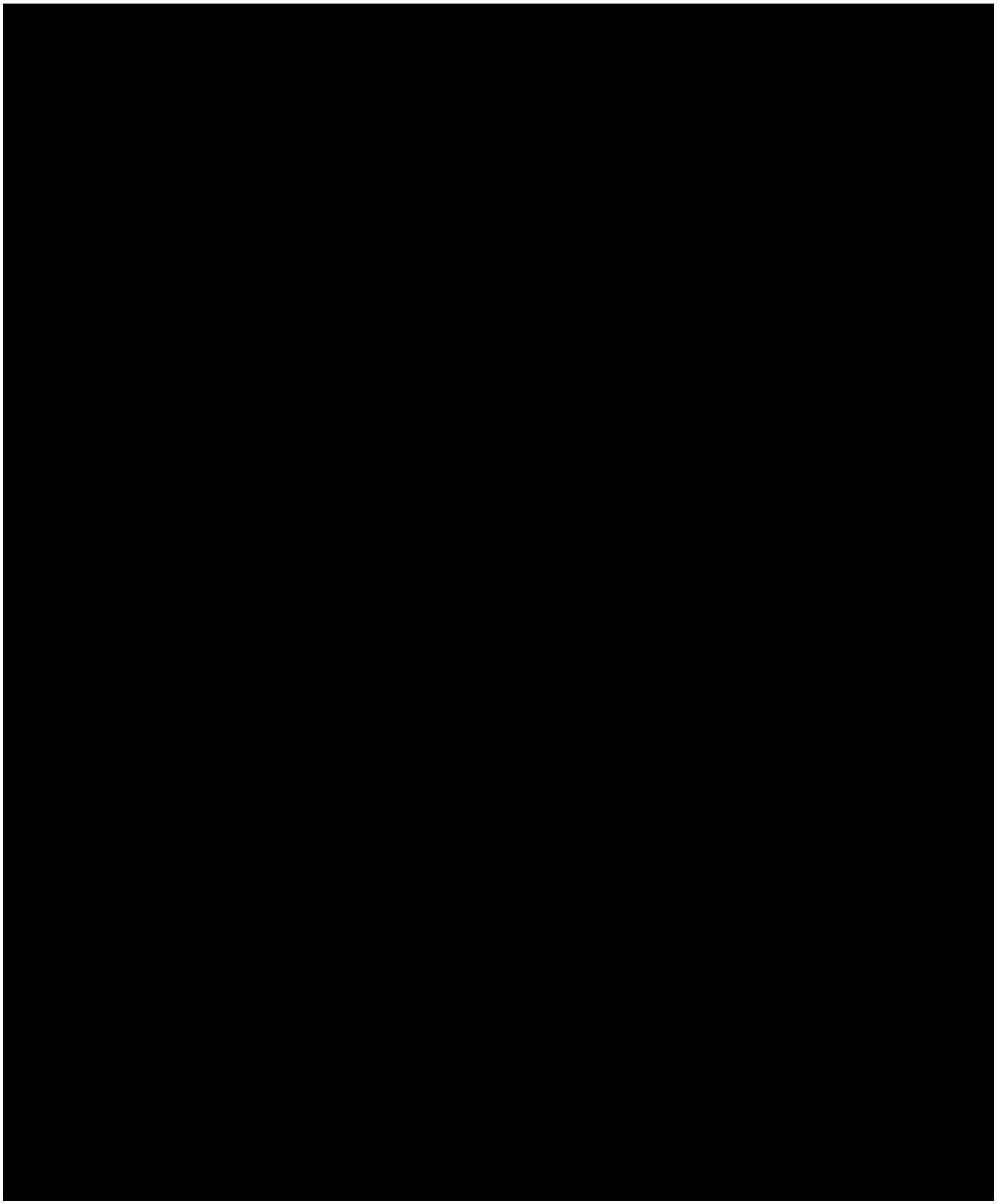
PK analyses are performed by a separate entity.

14.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of TFLs will follow ICH E3 guidance.

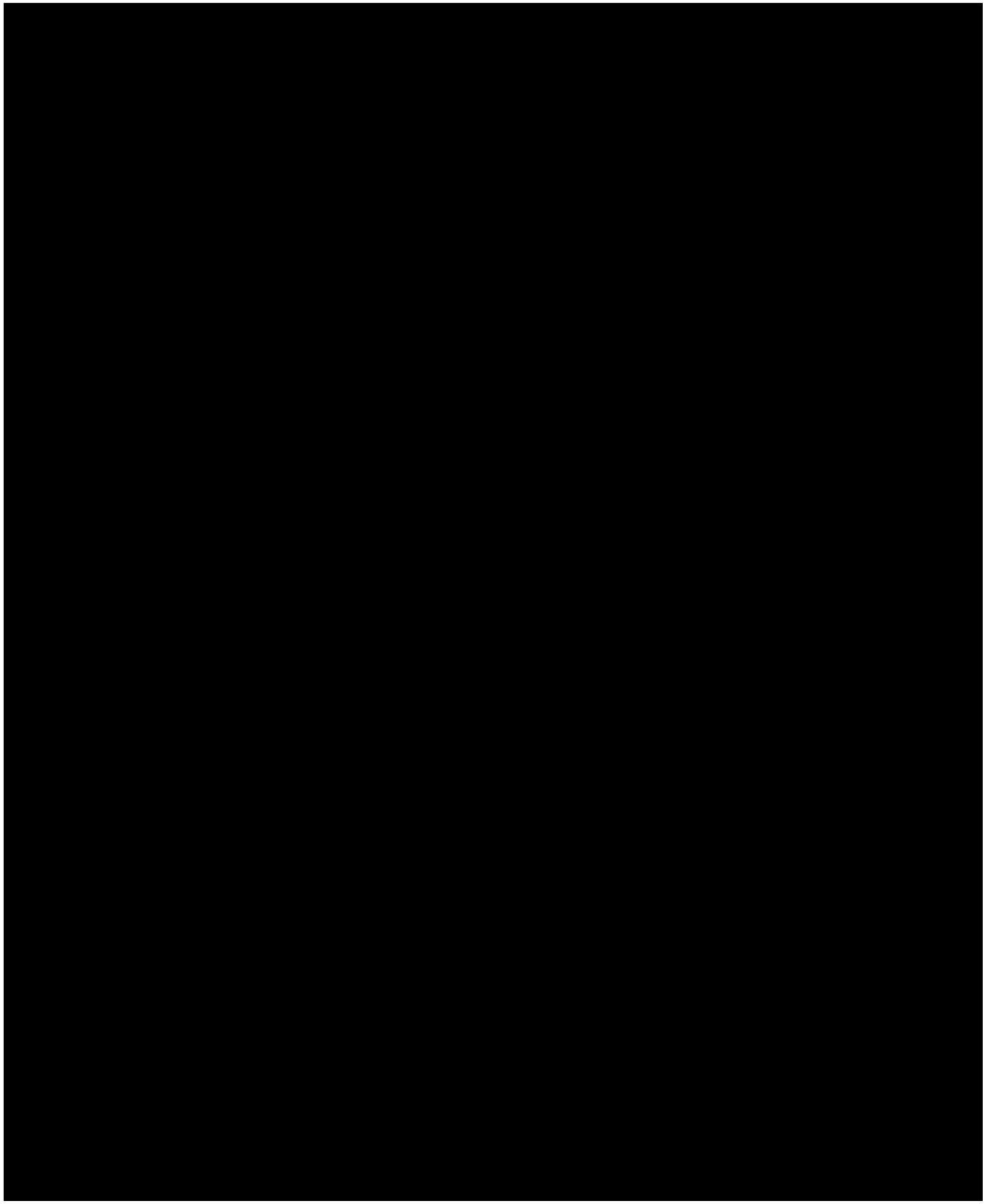


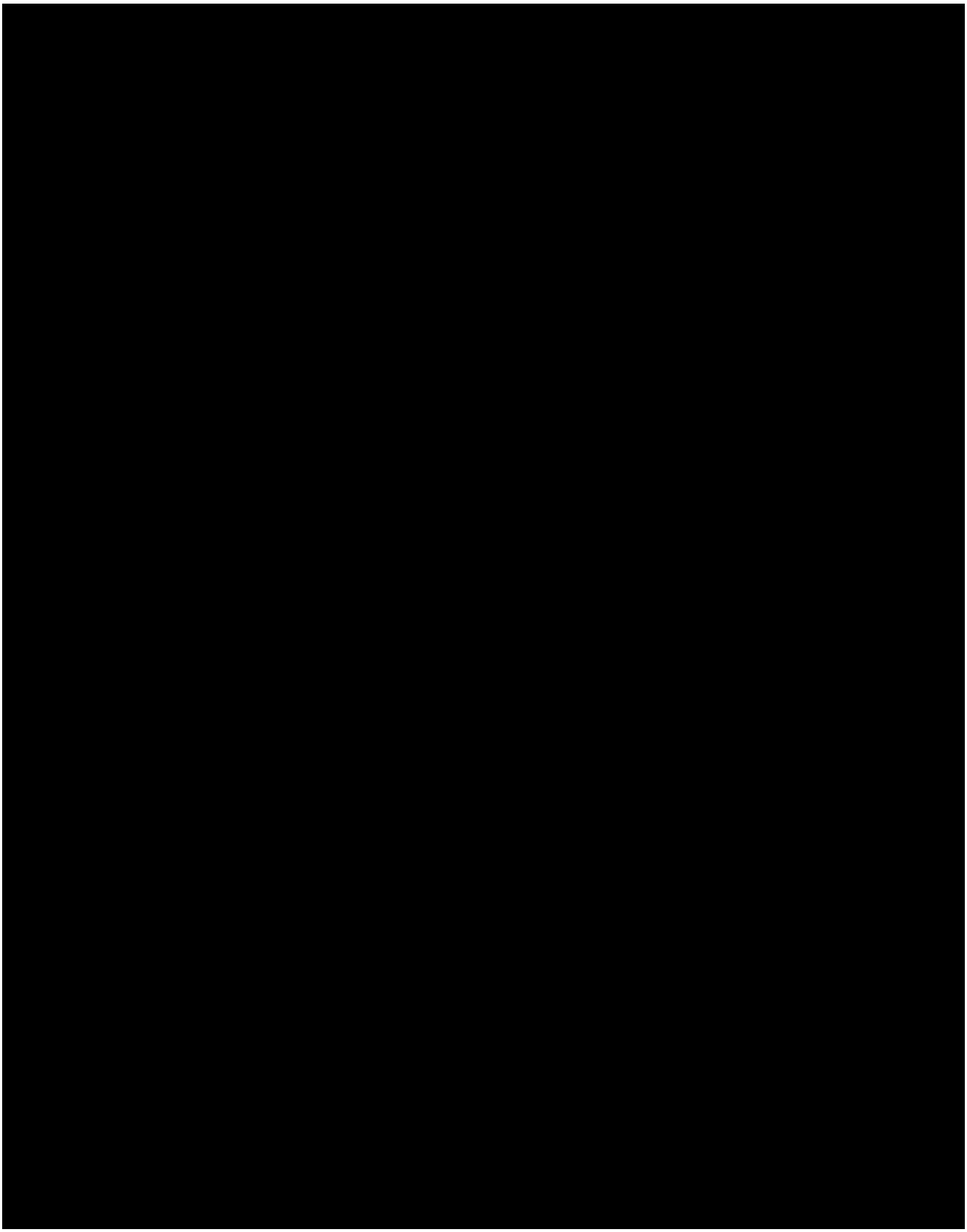


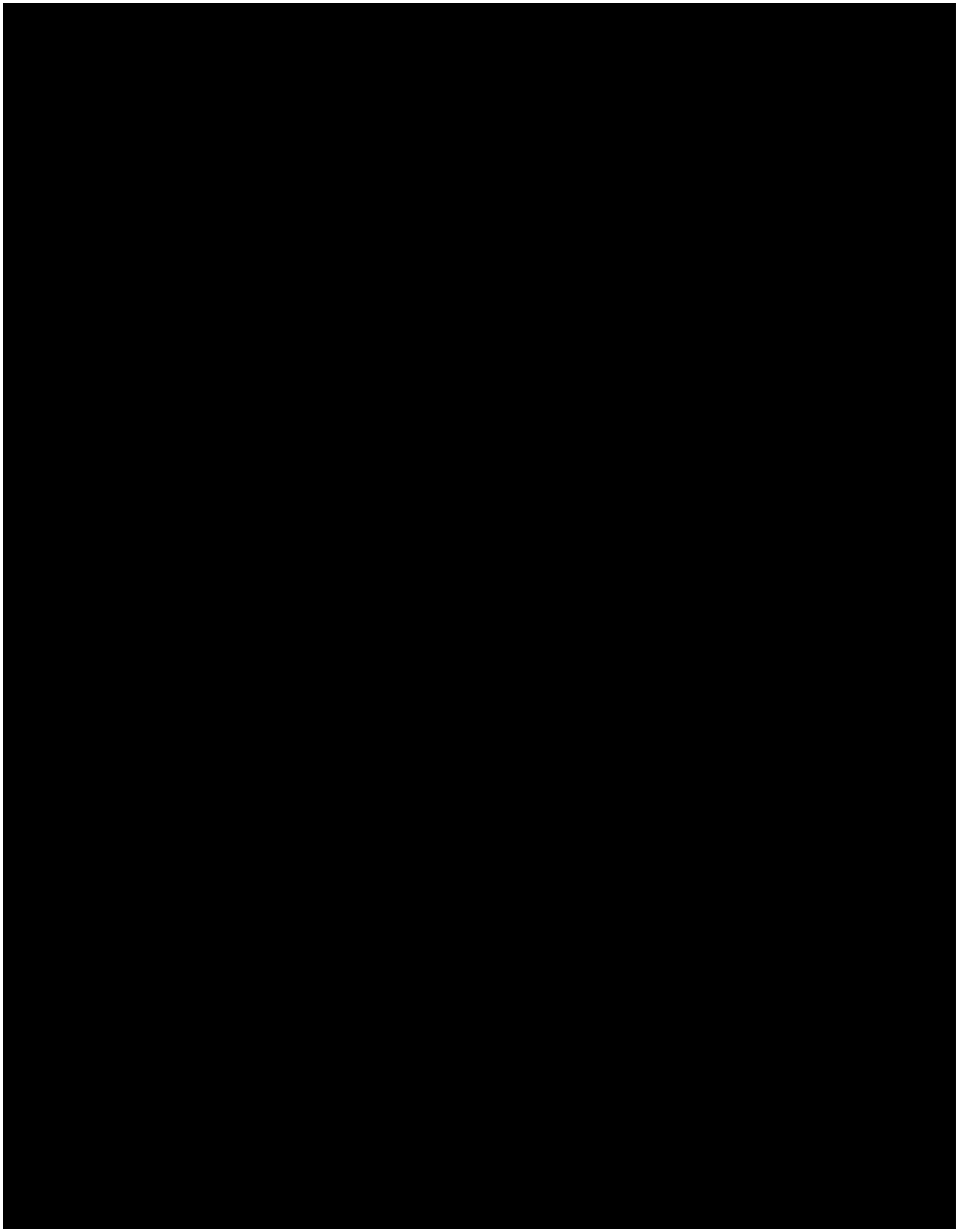


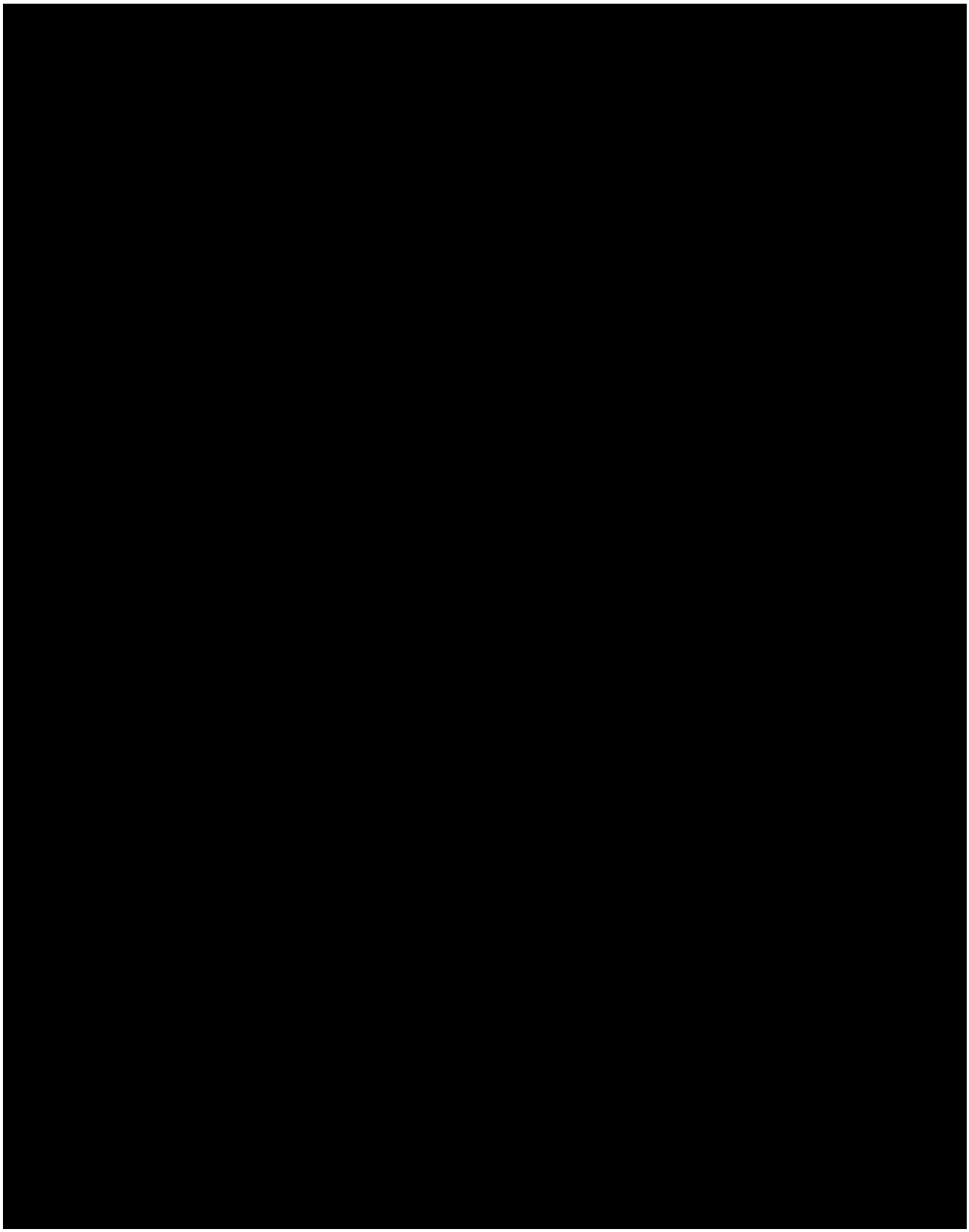
15. QUALITY CONTROL

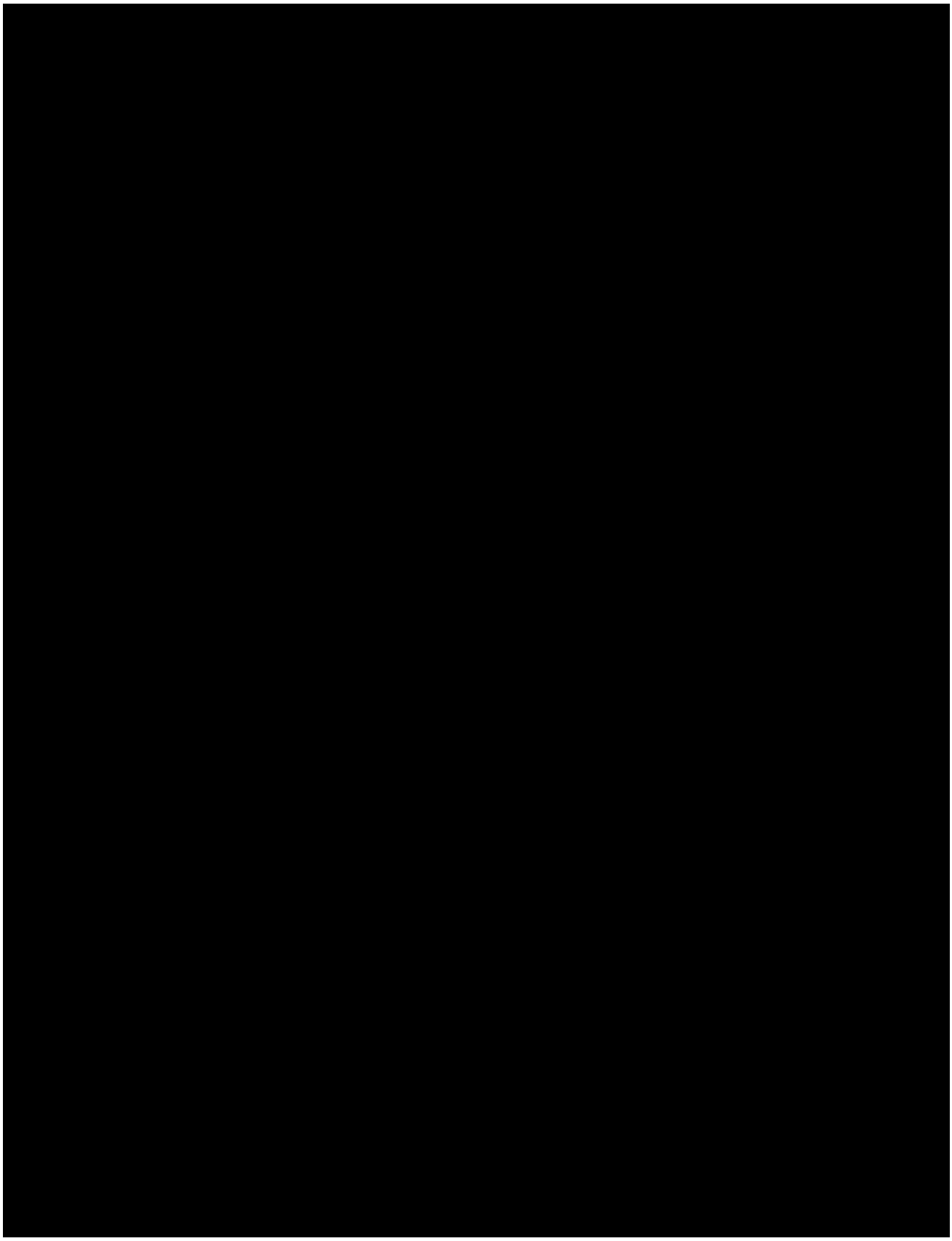
16. INDEX OF TABLES











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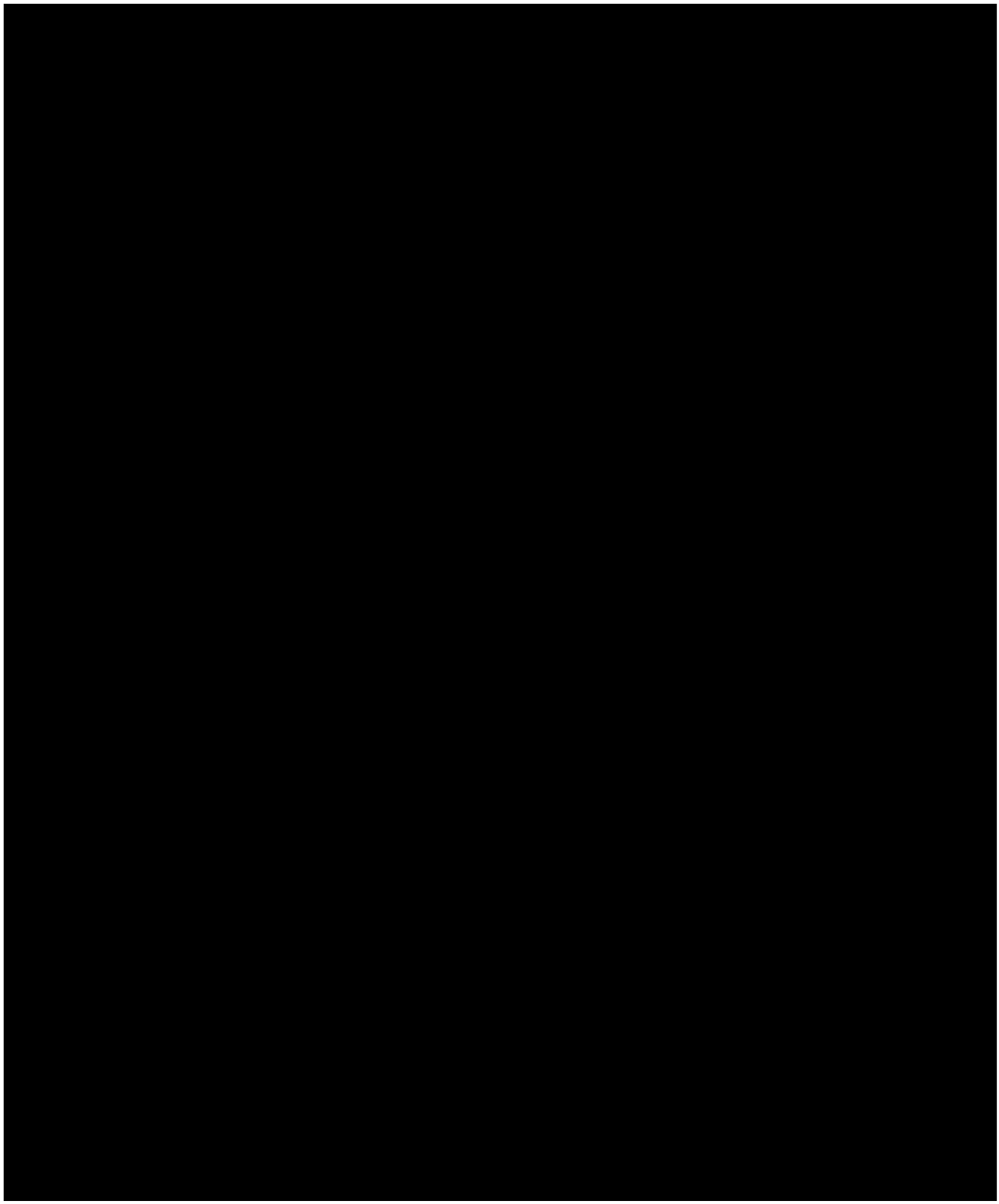

19. APPENDICES

19.1. Scoring the SF-36

Item (Question) Number	Number of Questions	Cumulative Question Number or Range
1	1	1
2	1	2
3	10 (a-j)	3-12
4	4 (a-d)	13-16
5	3 (a-c)	17-19
6	1	20
7	1	21
8	1	22
9	9 (a-i)	23-31
10	1	32
11	a-d	33-36

Scoring the SF-36: Step 1 - Recoding Items

Item numbers	Change Original Response Category*	To recoded value of:
1, 2, 20, 22, 34, 36	1→	100
	2→	75
	3→	50
	4→	25
	5→	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1→	0
	2→	50
	3→	100
13, 14, 15, 16, 17, 18, 19	1→	0
	2→	100
21, 23, 26, 27, 30	1→	100
	2→	80
	3→	60
	4→	40
	5→	20
	6→	0
24, 25, 28, 29, 31	1→	0
	2→	20
	3→	40
	4→	60
	5→	80
	6→	100
32, 33, 35	1→	0

	2→	25
	3→	50
	4→	75
	5→	100

*Precoded response choices as printed in the questionnaire

Scoring the SF-36: Step 2 – Averaging Items to Form Scales

Scale	Number of Items	After recoding average the following items	Item numbers on original questionnaire
Physical functioning	10	3, 4, 5, 6, 7,8, 9, 10, 11, 12	Qu. 3 a-j
Role limitations due to physical health	4	13, 14, 15, 16	Qu. 4 a-d
Role limitations due to emotional health	3	17, 18, 19	Qu. 5 a-c
Energy/fatigue	4	23, 27, 29, 31	Qu. 9 a, e, g, i
Emotional well-being	5	24, 25, 26, 28, 30	Qu. 9 b, c, d, f, h
Social functioning	2	20, 32	Qu. 6; Qu. 10
Pain	2	21, 22	Qu. 7; Qu.8
General health	5	1, 33, 34, 35, 36	Qu. 1; Qu. 11 a-d