Statistical Analysis Plan

ANB020-005

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING STUDY INVESTIGATING THE EFFICACY, SAFETY, AND PHARMACOKINETIC PROFILE OF ANB020 ADMINISTERED TO ADULT SUBJECTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan V1.1 (Dated 24OCT2019) for Protocol ANB020 -005.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

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1.0	19JUL2019		Sections have been renumbered. All section numbers below are from current numbering. Minor editorial changes throughout 5 Updated study design section to match protocol. 7.1 Added detail to DSMB section 7.2 Added Interim Analysis 8 Updated PPS definition 8.4 Added Windowing conventions table 8.9 Specified that data across sites will be pooled 8.10 Updated missing data strategy 8.11 Updated multiplicity strategy 10 Updated disposition reporting 11 Added list of major protocol deviations 15 Updated study medication exposure reports 16 Updated study and medication compliance definitions 17.1 Added primary endpoint definition statement of null and alternative hypotheses 17.1.1 Added multiple imputation description and updated primary endpoint analysis when using imputed data 17.1.2 Added description of sensitivity analysis 17.2 Added null and alternative hypotheses for Secondary efficacy endpoints and added definition of each secondary endpoint 17.2.2 Added missing data handling for SCORAD and DLQI 17.2.3 Updated analysis of secondary efficacy endpoints

			17.3 Added null and alternative hypotheses for exploratory efficacy endpoints and added definition of each exploratory efficacy endpoint 17.3.2.1 Added missing data handling for ACQ-6 17.4 Updated analysis of exploratory efficacy endpoints 18. Updated description of Safety outcomes 18.2 Updated description of death listing and summaries 18.6 Added description of physical examination reporting 19 Added PK endpoints
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below the lower limit of quantitation
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CS	Clinically significant
CTMS	Clinical trial management system
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
HR	Heart rate
IA	Interim analysis
LLOQ	Lower limit of quantitation
LS	Least squares
MCID	Minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
n	Sample size or number of observations
NCS	Not clinically significant
ND	Not determined

NRS	Numerical rating scale
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
POEM	Patient Oriented Eczema measure
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SI	System International
SOA	Schedule of Activities
SOC	System Order Class
TEAE	Treatment-emergent adverse event
vIGA-AD	Validated Investigator's Global Assessment for Atopic Dermatitis
WHO-DD	World Health Organization Drug Dictionary

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, pharmacokinetics (PK) and safety data for Protocol ANB020-005, Amendment 3, dated 02 July 2019. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the protocol.

The Data Safety Monitoring Board (DSMB) SAP, PK modeling and simulation plan, and Blinded Data Review Meeting plan will be separately created for this study.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the effects of etokimab on skin lesions

2.2. Secondary Objectives

- To evaluate the safety and tolerability of etokimab
- To evaluate the effects of etokimab on pruritus symptoms
- To evaluate the effects of etokimab on quality of life

2.3. Exploratory Objectives

- To evaluate the immunogenicity of etokimab
- To characterize the PK of etokimab
- To evaluate the effects of etokimab on asthma symptoms

3. ENDPOINTS

3.1. Primary Endpoint:

- Percent change in Eczema Area and Severity Index (EASI) score from Baseline to Week 16

3.2. Secondary Efficacy Endpoints:

At Week 16 and other clinical assessment time points, unless otherwise indicated:

- Proportion of subjects with EASI-50 (≥50% improvement from Baseline)
- Proportion of subjects with EASI-75 (≥75% improvement from Baseline)
- Proportion of subjects with EASI-90 (>90% improvement from Baseline)
- Proportion of subjects who achieve Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) score reduction of ≥2
- Proportion of subjects who achieve vIGA-AD response of 0 (clear) or 1 (almost clear)
- Proportion of subjects who achieve Numerical Rating Scale (NRS) for pruritus score[1] reduction from Baseline of ≥4
- Percent change in peak weekly averaged NRS for pruritus score[2] from Baseline
- Percent change in Scoring Atopic Dermatitis (SCORAD) scores from Baseline
- Change from Baseline in Dermatology Life Quality Index (DLQI)

Notes:

[1] Using NRS for pruritus "itch intensity weekly average"

[2] Using NRS for pruritus "maximum itch intensity"

For NRS please refer to section 8.1.6 in the protocol for more details

3.3. Safety and Tolerability Endpoints:

- Incidence of AEs
- Incidence of SAEs
- Incidence of treatment-emergent adverse events (TEAEs)
- AEs leading to discontinuation of study drug
- AEs leading to withdrawal from the study

- AEs resulting in death
- Changes in vital signs (blood pressure, temperature, respiration rate, heart rate [HR], and weight)
- Changes in clinical safety laboratory tests (haematology, chemistry, and urinalysis)
- Changes in electrocardiogram (ECG) parameters
- Immunogenicity (anti-drug antibody [ADA] and neutralizing ADA)

3.4. Exploratory Endpoints

- Absolute change in EASI score from Baseline to Week 16
- Percentage change in EASI score from Baseline to Weeks 4, 8, 12, 20, and 24
- Percent change in body surface area (BSA) from Baseline to Weeks 4, 8, 12, 16, 20, and 24
- Absolute change in percent BSA from Baseline to Weeks 4, 8, 12, 16, 20, and 24
- Change from Baseline in Asthma Control Questionnaire 6 (ACQ-6) Score at Weeks 4, 8, 12, 16, and 24
- Absolute change in SCORAD scores from Baseline to Weeks 4, 8, 12, 16, and 24
- Change from Baseline in Patient Oriented Eczema Measure (POEM) at Weeks 4, 8, 12, 16, 20, and 24
- Absolute change in POEM scores from Baseline
- Proportion of subjects with POEM change ≥ the minimal clinically important difference (MCID)
- Proportion of subjects with DLQI change ≥MCID
- Absolute change in peak weekly averaged NRS for Pruritus score from Baseline
- Absolute change in mean weekly averaged NRS for Pruritus score from Baseline
- Percent change in mean weekly averaged NRS for Pruritus score from Baseline
- Proportion of subjects with NRS change ≥MCID
- Proportion of subjects with EASI change ≥MCID
- Proportion of subjects with SCORAD change ≥MCID

3.5. Pharmacokinetic Endpoints (Exploratory):

A limited sampling strategy to collect samples of whole blood will be implemented for the determination of etokimab in human serum for PK assessment following subcutaneous (SC) administration. Pharmacokinetic concentration data collected from the study may be included in a population PK - based (meta-) analysis, using non-linear mixed effects modeling .

The PK endpoints for this study are as follows:

- Apparent clearance (CL/F) of etokimab
- Apparent volume of distribution (Vd/F) of etokimab
- Area under the curve (AUC_{τ}) for the first and last dose
- Maximum concentration (C_{max}) for the first and last dose
- T_{max} for the first and last dose
- $T_{1/2}$ for the last dose

4. HYPOTHESIS

4.1. Primary Hypothesis

Null Hypothesis (Ho): There are no differences between placebo treatment and any of the of the ANB020 treatment groups.

Alternative Hypothesis (Ha): At least 1 of the EASI scores in the ANB020 treatment groups is different from placebo.

Ho: $\delta_P = \delta_{E20/4} = \delta_{E300+150/4} = \delta_{E300+150/8} = \delta_{E600+300/4}$, ***vs.***

H_A: At least one $\delta_{Ti} \neq \delta_P$.

Please see Table 3.

Secondary Hypothesis

On the selected dose (general approach):

Ho: ANB020 treatment response = placebo response

Ha: ANB020 treatment response different than placebo response

General notation:

Ho: $p_0 = p_{E20/4} = p_{E300+150/4} = p_{E300+150/8} = p_{E600+300/4}$,

Ha: At least one $p_T \neq p_0$.

Note: similar approach for continuous endpoints

For each of the endpoints below (in parenthesis) the following secondary hypothesis (H_i) will be tested (in sequential order). The assumption is the same for each case as in general approach above):

- H_1 (Improvement in proportion of subjects with EASI-50 (≥50% improvement from Baseline))
- H_2 (Improvement in proportion of subjects with EASI-75 (≥75% improvement from Baseline))
- H_3 (Improvement in proportion of subjects with EASI-90 (≥90% improvement from Baseline))
- H_4 (Improvement in proportion of subjects who achieve vIGA-AD score reduction of ≥2)

- H_5 (Improvement in proportion of subjects who achieve vIGA-AD response of 0 or 1)
- H_6 (Improvement in proportion of subjects who achieve NRS for pruritus score reduction from Baseline of ≥ 4)
- H_7 (Percent change in peak weekly averaged NRS for pruritis score from Baseline)
- H_8 (Percent change in SCORAD score from Baseline)
- H_9 (Change from Baseline in DLQI)

5. STUDY DESIGN

5.1. General Description

This is a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, Phase 2b study designed to assess the efficacy of different doses and dose regimens of ANB020 (etokimab) compared to placebo in adult subjects with moderate to severe atopic dermatitis (AD). This study will also assess the efficacy, safety, tolerability, and PK of etokimab. This study will monitor the effects of etokimab on moderate to severe AD subjects over a period of 24 weeks.

The study will have a screening period of up to 4 weeks (Week -4 to 0) prior to administration of study drug on Day 1, a treatment period of 16 weeks (Week 0 to 16), and a safety follow-up period of 8 weeks (Week 16 to 24).

During the screening period, all subjects will undergo evaluation for eligibility. The subjects will be randomly assigned on Day 1 to one of the following 5 treatment groups in a 1:1:1:1:1 ratio as detailed in the protocol:

- Etokimab 20 mg SC every 4 weeks (Q4W)
- Etokimab 300 mg load + 150 mg SC Q4W
- Etokimab 300 mg load + 150 mg SC every 8 weeks (Q8W)
- Etokimab 600 mg load + 300 mg SC Q4W
- Placebo

The subjects will be administered study drug SC during onsite visits on Day 1 (Week 0), Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12). The subjects will remain on site for 2 hours for postdose assessments at Weeks 0, 4, 8, and 12. Additional visits will occur at Day 5 (Week 1), Day 15 (Week 2), Day 92 (Week 13), and Day 113 (Week 16) during the treatment period. For the safety follow-up visit, the subject will return to the study center on Day 141 (Week 20) and Day 169 (Week 24). The End of Study (EOS) visit will be on Day 169 (Week 24).

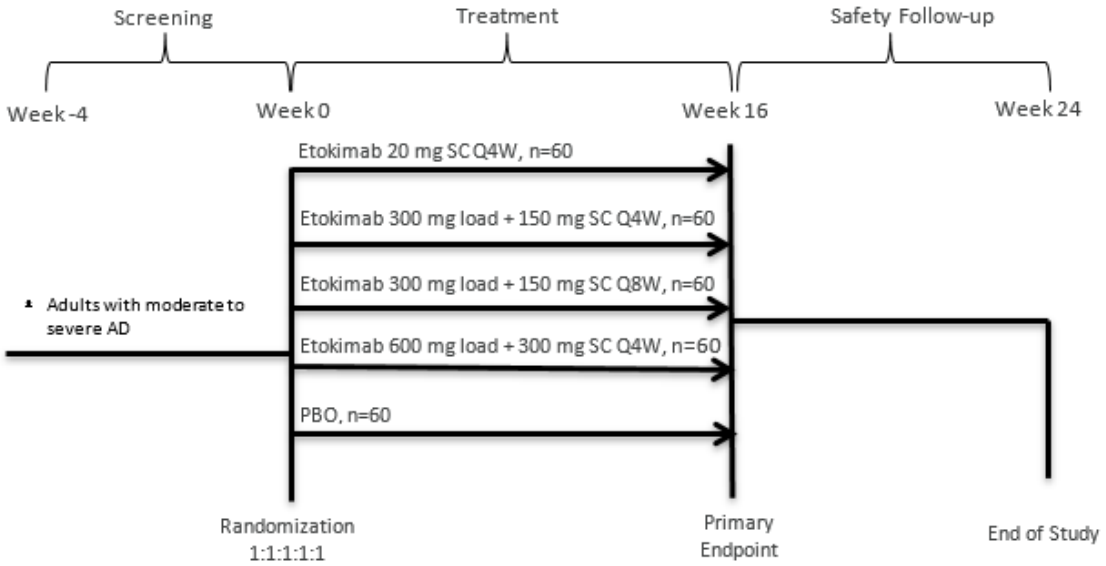
The subject's disease activity (response to study treatment) will be evaluated using the EASI, vIGA-AD, and SCORAD assessments. The patient-reported outcome measurements (POEM, ACQ-6, and DLQI) will be performed first at visits mentioned in the Schedule of Activities (SOA) before any other study procedures (except informed consent at the screening visit). Dermatology Life Quality Index and POEM questionnaires will be administered only to the subset of subjects who can read and understand a language in which questionnaire is presented (based on availability of validated translations in participating countries). The ACQ-6 will be assessed only in subjects with active asthma disease whose primary language is a language in which questionnaire is presented (based on availability of validated translations in participating countries). The NRS for pruritus, also a patient-reported outcome measurement, will be completed daily via an electronic

patient reported outcomes device.

Serum samples for PK and immunogenicity will be collected before the administration of study drug and at the other time points specified in the SOA. Safety assessments including adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examination, ECGs, and laboratory measurements will be performed as specified in SOA. A DSMB will be instituted to periodically review and evaluate the study data for subject's safety and advise the Sponsor of potential safety signals.

A study schematic for Protocol ANB020-005 is presented in Figure 1.

Figure 1 Study Schematic



Abbreviations: AD = atopic dermatitis; PBO = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneously

5.2. Sample Size

The expected efficacy response (and variability) for active and placebo response (related with percent change from Baseline in EASI score to Week 16) was estimated after review of 5 previous studies in subjects with moderate to severe AD subjects not taking topical corticosteroids.

In this way, in an analysis of covariance design, a total sample of approximately 300 subjects (60

subjects per treatment group) achieves more than 95% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05000 significance level. The size of the variation in the means is represented by their standard deviation which is 18.59. The common standard deviation within a group is assumed to be 50.00.

The hypothesized means used to compute the sample size derived from the studies mentioned before are: -20 -44. -65.4 -66.4 -68 (for placebo and each active treatment group respectively) with a covariate R-squared of 0.300.

5.3. Schedule of Events

The SOA can be found in Section 1.3 of the protocol.

5.4. Changes to Analysis from Protocol

There are no changes from the analysis mentioned in the protocol.

6. STATISTICAL GENERAL CONSIDERATIONS

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor and in consistency with this SAP. Data for patients excluded from an analysis set will be included in the data listings, but not in the summaries.

Coding of AEs and medical history will be done by Medical Dictionary for Regulatory Activities (MedDRA) directory Version 22 (or higher) and medications data by the World Health Organization (WHO)-drug dictionary dated Mar2019 (or higher) by IQVIA™.

The terms "change from Baseline" and "absolute change from Baseline" are used interchangeably throughout this document.

The default summary statistics for continuous variables includes number of contributing observations (n), mean, standard deviation (SD), median, minimum, and maximum or as described in the respective section. For categorical variables, the number and percentage (the percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number of subjects in the relevant analysis set, with assessments available [where appropriate]) in each category will be the default summary presentation.

In general, for non-PK data, the number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.
- SD: 2 more than the number of decimal places allotted in the raw data.
- Minimum and maximum: equal to the number of decimal places allotted in the raw data.
- Percentages: All percentages between 0 and 100 will be rounded to 1 decimal unless there is a need to report more than 1 decimal for percentages.
- Reference ranges will be reported to the same number of decimal places displayed by the laboratory.
- *P* values and confidence intervals (CIs), if any, will be reported to 4 decimal places. *P* values less than 0.0001 will be presented as "<0.0001" and *p* value greater than 0.9999 will be presented as "1.0000".

The following descriptive statistics by treatment (dose amount/schedule) and nominal study day will be presented in summary tables for the etokimab concentrations obtained in this study: number of non-missing observations (n), mean, SD, coefficient of variation (CV), minimum, median, and maximum. For etokimab concentrations, the number of observations above or equal to the lower limit of quantitation (LLOQ) will also be included.

Concentration versus time summaries will be presented for all patients in the PK Analysis Set

(described in Table 1 Analysis Sets

Data from patients excluded from an analysis set will be included in the data listings, but not in the summaries.

For etokimab concentration results, the data will be rounded as follows:

- Etokimab concentrations will be reported in listing(s) and analyzed with the same precision as the source data regardless of how many significant figures or decimal places the data carry. Reporting of mean, SD, and median will carry 1 more significant figure/decimal place than the source data, according to the precision method used for source data.
- Minimum and maximum will carry the same number of significant figures/decimal places as the source data.
- Coefficient of variation will be reported to 1 decimal place.
- Pharmacokinetic elapsed time variables will be reported with 2 decimal places with units of hours.

Analysis plans for population PK modeling and potential pharmacodynamic (PD) and/or efficacy/safety correlative exploratory analyses will be described further in a separate modeling and simulation analysis plan. Results from any population PK analysis and correlation with PD/efficacy/safety results will be presented separately from the main clinical study report in a PK modeling and simulation report.

7. PLANNED ANALYSIS

7.1. Data Safety Monitoring Board

A DSMB consisting of independent physicians and statisticians who are not Investigators in the study and who do not have a perceived conflict of interest with the conduct and administration of the study will be convened on a regular basis to evaluate the clinical study progress and review AEs. A DSMB SAP, describing the methodology and presentation of results and access to results, will be provided by IQVIA Biostatistics as a separate document. The data review meetings (DRMs) will follow the following schedule:

- DSMB DRM #1 approximately 25% enrolment
- DSMB DRM #2 approximately 50% Treatment Completers
- DSMB DRM #3 100% W16 Treatment Completers (planned directly after interim analysis [IA] with IA data)
- DSMB DRM #4 Final Data – 100% W24 completion of study

7.2. Interim Analysis

An IA will be performed when all active subjects complete their Week 16 visit which will be considered the final assessment of all primary and secondary efficacy endpoints (for Week 16). The IA will also consider all safety data available (up to Week 24).

7.3. Final Analysis

The Final Analysis (final database lock) will be executed once all subjects complete their Week 20 and Week 24 safety and exploratory efficacy assessments and efficacy assessments for the primary and secondary endpoints will be re-executed, reporting Baseline, Week 16, Week 20, and Week 24 results.

The PK summaries, data listings, and PK figures will be the responsibility of the PK biostatistician at IQVIA.

8. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set (Table 1 below) will be conducted prior to the unblinding of the study for the IA to be performed when all subjects complete their safety and efficacy Week 16 assessments.

Table 1 Analysis Sets

Analysis Set	Description
Safety Analysis Set (SAF)	The SAF will include all randomized subjects who receive at least 1 dose of etokimab or placebo. The SAF will be used for all safety analyses. Subjects will be analyzed as treated.
Full Analysis Set (FAS)	The FAS will be based on the intent to treat principle and will include all randomized subjects who receive at least 1 dose of etokimab or placebo and have Baseline and postbaseline EASI score. The FAS will be used for all efficacy analyses. Subjects will be analyzed as randomized.
PP Analysis Set (PPS)	The PPS will include all subjects in the FAS who do not have major protocol deviations (See Section 10.1.10 in the Protocol).
Pharmacokinetic (PK) Analysis Set	The PK Analysis Set will include all etokimab treated subjects in the safety analysis set who have at least one quantifiable postdose PK sample available and who do not have events or protocol deviations with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses. The PK analysis is defined in detail in the Pharmacometric Plan.

Additionally, Screen Failure (SF) patients are all patients who were screen failures and not randomized or dosed.

8.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date)

- In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

8.2. Baseline

The last nonmissing predose measurement taken prior to etokimab or placebo administration at randomization [Day 1] will be considered the baseline value.

For NRS (numerical rating scale) for pruritus which will be completed daily via ePRO device (see details in section 8.1.6 in the protocol), two baseline average values will be computed: one for the baseline average itch intensity, and the second one for the maximum itch intensity (or peak weekly average NRS at baseline.

For all safety variables, Baseline will be last nonmissing measurement taken prior to reference start date (including unscheduled assessments or retests). If the predose measurement and the reference start date coincide, that measurement will be considered Baseline.

8.3. Retests, Unscheduled Visits, and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. In the case of a retest (same visit number is assigned), the latest available measurement for that visit will be used for by-visit summaries. Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data collected in the electronic case report form (eCRF).

8.4. Windowing Conventions

Visit windows are assigned based on the Protocol SOA are presented in

Table 2.

Table 2 Visit Windows

Assigned Visit	Assigned Study Week	SOA day(s)	Study day(s)
1 (Screening)	-4 to 0	-28 to 0	-28 to 0
2 (Treatment)	0	1	1
3 (Treatment)	1	5 ± 1d	4 to 6
4 (Treatment)	2	15 ± 2d	13 to 17
5 (Treatment)	4	29±2d	27 to 31
6 (Treatment)	8	57±3d	54 to 60
7 (Treatment)	12	85±3d	82 to 88
8 (Treatment)	13	92±5d	87 to 97
9 (Treatment)	16	113±5d	108 to 118
10 (Safety Follow-Up)	20	141±5d	136 to 146
11 (Safety Follow-Up)	24/EOS/ET	169±5d	164 to 174

8.5. Statistical Tests

The default significance level will be 0.05 two-sided; CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

8.6. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

Percentage change from baseline will be calculated as:

- (Test Value at Visit X – Baseline Value) *100/ Baseline Value

8.7. Software Version

All analyses, statistics, and graphics reported in the clinical study report (including etokimab concentrations) will be conducted using Statistical Analysis System® (SAS) Version 9.4 or higher (SAS-Institute, Cary, North Carolina, USA).

8.8. Adjustments for Covariates and Factors to be Included in Primary and Secondary Analyses

The following covariates are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline EASI score
- Baseline vIGA-AD score
- Baseline NRS score
- Baseline SCORAD
- Baseline DLQI score

The following factors are used in the analyses.

- Treatment
- Visit

8.9. Multicenter Studies

Study centers across the United States, Canada, and Europe are expected to participate in this study. Data from all sites will be pooled for analysis.

8.10. Missing Data

For duration of disease and birth date, the missing date will not be imputed. Missing safety data will not be imputed. Partial dates will be imputed as per APPENDIX 2.

Missing efficacy data will be imputed using multiple imputation (MI) method described in Section 17.1.1. Missing data will be imputed in a single step for all visits. For reporting and analysis, analysis models will be run “by visit”.

For subjects who receive chronic rescue therapy and are considered non-responders according to protocol Section 6.5.2 (Rescue Medicine), the data collected after rescue therapy is initiated will be treated as missing. In addition, secondary and exploratory endpoints with responder/non-responder outcomes will have data treated as missing after discontinuation due to chronic rescue

medication use. However, their endpoint outcome will be defined as non-responder according to the date chronic rescue medication began.

If a subject has acute rescue medication use, they will not be considered as non-responder by this criterion and all of their data will be used in the analysis. Rescue medication use that meets the threshold of non-responder, as defined in protocol section 6.5.2, are considered 'chronic' use. If it does not meet the threshold, it is considered 'acute' use.

Details about missing data for primary and secondary endpoints are detailed in sections 17.1.1 and 17.3.1 respectively. Assessments with missing data will be handled per the instructions provided by the author for each particular instrument, as described in Sections 17.2.1 and 17.3.1. Missing PK data will be handled as described in Section 19 of this plan.

8.11. Testing Strategy and Adjustment for Multiplicity

8.11.1. Testing Strategy for the Primary Endpoint

For the primary endpoint, a hierarchical testing procedure will be used, from the highest dose to the lowest dose until statistical significance at the 5% alpha level is not achieved. Hierarchical testing will occur in the following order:

Table 3 Hierarchical Order of Treatment Groups for Testing Strategy for Primary Endpoint at Week 16

Sequence	Arms to compare		Alpha Level
1	Etokimab 600 mg load + 300 mg SC Q4W	Vs. Placebo	0.05
2	Etokimab 300 mg load + 150 mg SC Q4W	Vs. Placebo	0.05
3	Etokimab 300 mg load + 150 mg SC Q8W	Vs. Placebo	0.05
4	Etokimab 20 mg SC Q4W	Vs. Placebo	0.05

Note: comparisons between active treatment doses are not intended in this study. In case that 2 or more dose levels results are positive then the Sponsor will select the optimal dose based on the risk / benefit profile for each dose level.

8.11.2. Testing of Secondary Endpoints:

A gatekeeping procedure in the primary endpoint will be used, only if at least 1 comparison between active treatments vs placebo for the primary endpoint crosses the $\alpha = 0.05$ boundary for statistical significance, then the secondary endpoints will be tested in a hierarchical approach. For

example:

- If the *p* value for the comparison between etokimab 300 mg load + 150 mg SC Q4W vs placebo is equal or smaller than 0.05 then:

The secondary hypothesis (mentioned also in Section 4) will be tested sequentially.

That is, for each of the j= 1, 2, …, 9 secondary hypotheses,

If nominal *p* value $H_1 < 0.05$, reject H_1 and continue with H_2; else stop.
If nominal *p* value $H_2 < 0.05$, reject H_2 and continue with H_3; else stop
If nominal *p* value $H_3 < 0.05$, reject H_3 and continue with H_4; else stop
If nominal *p* value $H_4 < 0.05$, reject H_4 and continue with H_5; else stop
If nominal *p* value $H_5 < 0.05$, reject H_5 and continue with H_6; else stop
If nominal *p* value $H_6 < 0.05$, reject H_6 and continue with H_7; else stop
If nominal *p* value $H_7 < 0.05$, reject H_7 and continue with H_8; else stop
If nominal *p* value $H_8 < 0.05$, reject H_8 and continue with H_9; else stop
If nominal *p* value $H_9 < 0.05$, reject H_9 and stop

8.12. Examination of Subgroups

Subgroup analyses may be performed as deemed appropriate. Any subgroup analysis will be considered Post Hoc.

Subgroups may include, but are not limited to:

- Age group
- 18 to <50
- 50 to <75
- Gender
- Race
- Region
- Disease status at Baseline
- Moderate
- Severe
- Pruritis NRS at Baseline
- ACQ-6 at Baseline

9. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and, therefore, the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

All visit assessments will be presented according to the nominal visit name. For reporting and analysis of endpoints with imputed data, models will be run and presented "by visit".

10.DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Subject disposition will be listed and summarized, including:

- Total subjects screened
- Number of screen failures (subjects who consent to participate in the clinical study but are not subsequently entered in the study)
- Total of subjects in the FAS by treatment group
- Total subjects randomized, but not treated by treatment group
- Total subjects randomized and treated by treatment group
- Total subjects ongoing (subjects ongoing at the time of the IA) by treatment group
- Total number of subjects in the SAF by treatment group
- Total number of subjects in the PPS
- Total number of subjects in the PK Analysis Set
- Total subjects who discontinue from study treatment by treatment group
- Total subjects who discontinue from the study by treatment group
- Total number of subjects who received chronic rescue medication by treatment group
- Major protocol deviations and inclusion and exclusion criteria

11.PROTOCOL DEVIATIONS

All protocol deviations observed during study conduct will be captured in the Clinical Trial Management System (CTMS).

The Investigator and Sponsor will review the protocol deviation records from the CTMS and provide confirmation on the categorization of deviations.

Categorization definitions per the Protocol Deviation Plan are:

Critical: A deviation from protocol-related procedures that threatens integrity of data, adversely affects subjects, and/or could invalidate acceptability of a project (or part of it). Such deviations require immediate action.

Major: A deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects. Such deviations require timely action.

Minor: A deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately.

Major protocol deviations considered to affect the primary analysis include, but are not limited to, the following:

Table 4 List of Major Protocol Deviations

No.	PD Group	PD Description
01	Eligibility and Entry Criteria	Not meeting either inclusion or exclusion criteria (at time of randomization)
02	Informed Consent	Informed consent not signed
03	Compliance with Study Treatment	Mishandling of the study drug which could have impacted the integrity of the study data such as non-allowable temperature deviations during storage or dispensing of study drug to the wrong subject
04	Compliance with Study Treatment	Partial dosing of study treatment
05	Concomitant Medications	Use of prohibited concomitant medications unless defined as rescue medication per protocol
06	Study Procedures	Study procedures done outside protocol-specified window period that are judged to affect study efficacy data.

No.	PD Group	PD Description
		Critical Protocol Deviations captured via CTMS will also be included.
07	Study Procedures/PK1	Changes to the procedures or events which may impact the quality of the PK data will be considered significant protocol deviations or events and will be described within the clinical study report body text

Note:

These deviations or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results and/or inaccurate/incomplete dosing for a dosing interval for which PK samples are collected. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations.

A frequency table for major protocol deviations will be provided for the SAF.

Major protocol deviations or events that impact the quality of the PK and/or PD data will be listed only.

12.DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be listed and summarized for the SAF. No statistical testing will be carried out for demographic or other baseline characteristics data.

- Summary statistics will be provided for:
  - Age (years)
  - Weight (kg)
  - Height (cm)
  - Body Mass Index (BMI [kg/m^2])
- Frequency tables will be provided for:
  - Gender
  - Women of child bearing potential
  - Ethnicity
  - Race
- Continuous variables will be summarized using count, mean, SD, median, minimum, and maximum
- Categorical variables will be summarized using frequency and percentage
- Separate summary table by EU states will be provided for European (EU) patients
- Derivations
  - BMI (kg/ m^2) = weight (kg)/ [height (m)]^2

13.MEDICAL HISTORY

Medical history is collected only at Screening and will be listed and summarized for all the subjects by system organ class and preferred term.

14.CONCOMITANT THERAPIES

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

Prior medications are subcategorized as Prior to Randomization and Prior Atopic Dermatitis Therapies.

Concomitant medications are subcategorized as: Post randomization and rescue therapies.

These will be reported in separate listings.

See APPENDIX 2 for handling of partial dates for medications. In case it is not possible to define a medication as prior or concomitant, the medication will be classified conservatively as concomitant.

15. STUDY MEDICATION EXPOSURE

Duration of treatment exposure, average weekly and total dose will be listed and summarized by treatment groups using the SAF.

15.1. Derivations

Duration of treatment exposure (weeks) = (Truncate (Date of last study medication administration – Date of first study medication administration)/7) + 4 weeks.

16.COMPLIANCE

16.1. Compliance with Study Medication

The assigned dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be captured in the eCRFs and recorded as protocol deviations. Investigational Product Compliance will be listed and summarized, including number of subjects with planned and actual treatment for each visit.

Missing the loading dose will result in discontinuation from the study.

16.2. Compliance with the Protocol

Subjects who miss 2 consecutive doses after the loading dose will be discontinued from the study unless these subjects have received chronic rescue medication according to Section 6.5.2 of the protocol.

Treatment compliance will be descriptively summarized by treatment group for the SAF, including the number and percentage of subjects who miss each assigned dose and number and percentage of subjects who are discontinued from the study due to one or more missed doses.

17.EFFICACY ENDPOINTS

17.1. Primary Efficacy Endpoint

Percent change in EASI score from Baseline to Week 16 will be analyzed using the FAS.

Let the change (δ) from Baseline (B) in EASI at Week 16 (W16) be denoted for placebo (P) and each active treatment (T_i) group as:

$\delta_P = EASI_{W16,P} - EASI_{B,P}$ and

$\delta_T = EASI_{W16,Ti} - EASI_{B,Ti}$.

Further, let each active treatment group (T_i) be denoted as:

E20/4: Etokimab 20 mg SC every 4 weeks (Q4W)

E300+150/4: Etokimab 300 mg load + 150 mg SC Q4W

E300+150/8: Etokimab 300 mg load + 150 mg SC every 8 weeks

E600+300/4: Etokimab 600 mg load + 300 mg SC Q4W

Then the null and alternative hypotheses are stated as:

Ho: $\delta_P = \delta_{E20/4} = \delta_{E300+150/4} = \delta_{E300+150/8} = \delta_{E600+300/4}$, ***vs.***

H_A: At least one $\delta_{Ti} \neq \delta_P$.

17.1.1. Missing Data Methods for Primary Efficacy Endpoint

Missing efficacy data for the primary endpoint will be handled using a MI procedure as follows:

Step 1 – Imputation Phase:

a. Creation of monotone missing data structure using 50 interactions (M), to ensure that the final results do not suffer from a relative efficiency loss (Van Buuren, 2012 cited by Patricia Berglund and Steven Heeringa in Multiple imputation using SAS 2014.):

Intermediate (non-monotone) missing data (where some subjects may have missing records) will be imputed using the Markov Chain Monte Carlo (MCMC) method including treatment_arm, EASI_Baseline, EASI_Week1, EASI_Week2, EASI_Week4, EASI_Week8, EASI_Week12, and EASI_Week16 and assuming that the joint distribution of these variables is multivariate normal and the pattern for missing data is arbitrary. For this step the SAS procedure PROC MI with the MCMC option will be used.

b. Further imputations:

The datasets, now with monotone missing data, will be imputed further, in a step-wise manner to impute each week's EASI from Week 1 to Week 16 using the regression method (assuming missing at random). The model for each week will include terms for all of the previous weeks and follow the structure of the following model for each visit.

Step 2 – Analysis Phase

At this stage there are 50 imputed datasets with no missing data. For each imputed dataset, calculate the percent change in EASI score from Baseline to Week 16 and analyze using an analysis of covariance (ANCOVA) model adjusting for baseline EASI score (EASI_B). The primary comparison will be least squares (LS) mean difference between active treatment group(s) and placebo at 16 weeks. Treatment differences will be presented with corresponding *p* values and 95% confidence interval (CI).

Step 3 – Estimation and Inference for Imputed Data Sets

This step will aim to perform a compute multiple imputation estimates of the descriptive statistics, model parameters and the variance of the MI estimates (computed in step 2) using Proc MIANALYZE. The pooled treatment difference, 95% CI, and *p* value will be reported.

17.1.2. Sensitivity Analysis for the Primary Efficacy Endpoint

17.1.2.1. Sensitivity analysis using the PPS

The first sensitivity analysis will be performed as described for the primary efficacy analysis in Section 17.1, but using the PPS. Missing data approach will be the same as for the primary analysis.

17.1.2.2. Sensitivity analysis using Worst-Case Imputation method (FAS)

The second sensitivity analysis will use the FAS and worst-case imputation method. All subjects with missing data for Week 16 EASI will be imputed with their worst EASI score (including Baseline value).

17.1.2.3. Sensitivity analysis after chronic rescue medication (FAS)

To measure the impact on treatment effect of treating data as missing for those subjects who met the criteria of non-responder as the result of chronic rescue medication use, a sensitivity analysis using the FAS with all EASI data after initiation of chronic rescue medication will be performed. Missing data will be handled using the same approach as for the primary endpoint.

17.2. Secondary Efficacy

For the interim analysis, reporting will reflect the time points through Week 16. For the final

analysis, tables will include Baseline value and either Week 16 through Week 24 or Weeks 16, 20, and 24, as appropriate.

Preliminaries:

let p_0= the proportion of subjects achieving the benchmark in the placebo group and
p_T= the proportion of subjects achieving the benchmark in a treatment group.
Then
Ho: $p_0 = p_{E20/4} = p_{E300+150/4} = p_{E300+150/8} = p_{E600+300/4}$,
H_A: At least one $p_T \neq p_0$.

Proportion of subjects with EASI-50 (≥50% improvement from Baseline)

For each subject, define
EASI50= 1 if [100*(EASI_16 – EASI_B)/ EASI_B] ≥ 50, 0 otherwise,
where
EASI_B = EASI at Baseline and EASI_16 = EASI at Week 16.
EASI50 = 1 if subject achieved ≥50% improvement from Baseline, 0 otherwise.
Then P_EASI50 for each treatment group is (Σ EASI50)/n.

Proportion of subjects with EASI-75 (≥75% improvement from Baseline)

For each subject, define
EASI75= 1 if [100*(EASI_16 – EASI_B)/ EASI_B] ≥ 75, 0 otherwise,
where
EASI_B = EASI at Baseline and EASI_16 = EASI at Week 16.
EASI75 = 1 if subject achieved ≥75% improvement from Baseline.
Then P_EASI75 for each treatment group is (Σ EASI75/n).

Proportion of subjects with EASI 90 (≥90% improvement from Baseline)

For each subject, define
EAS90= 1 if [100*(EASI_16 – EASI_B)/ EASI_B] ≥ 90, 0 otherwise,
where
EASI_B = EASI at Baseline and EASI_16 = EASI at Week 90.
EASI90 = 1 if subject achieved ≥90% improvement from Baseline.
Then P_EASI90 for each treatment group is (Σ EASI90/n).

Proportion of subjects who achieve vIGA score reduction of ≥2

For each subject, define
VIGA2= 1 if (VIGA_16 – VIGA_B) ≥ 2, 0 otherwise,
where
VIGA_B = vIGA at Baseline and VIGA_16 = vIGA at Week 16.
VIGA2 = 1 if subject achieved ≥2 improvement from Baseline, 0 otherwise.

Then P_VIGA2 for each treatment group is (Σ VIGA2)/n.

Proportion of subjects who achieve vIGA-AD response of 0 (clear) or 1 (almost clear)

For each subject, define
VIGA01= 1 if VIGA_16 ∈ (0,1), 0 otherwise,
where
VIGA_16 = vIGA at Week 16.
VIGA01 = 1 if subject achieved vIGA = 0 (clear) or 1 (almost clear), 0 otherwise.
Then P_VIGA01 for each treatment group is (Σ VIGA01)/n.

Proportion of subjects who achieve NRS for Pruritus score reduction from Baseline of ≥4

For each subject, define
NRSP4= 1 if (NRSP_16 – NRSP_B) ≥ 4, 0 otherwise,
where
NRSP_B = NRS for Pruritis score at Baseline and
NRSP_16 = NRS for Pruritis score at Week 16.
Then P_NRSP4 for each treatment group is (Σ NRSP4)/n.

Percent change in peak weekly averaged NRS for Pruritus score from Baseline

For each subject and week, define
NRSP_peak_avg= $\left(\sum_{i=1}^{k} Peak\ NRS\ for\ Pruritis\ on\ Day\ i\right)/k$,
where
k = number of days NRS for Pruritis score was recorded for that week.
Then for weeks $j = 2, \ldots, 16$,
NRSP_peak_Pct_Chg = (NRSP_ peak_avg – NRSP_B) * 100 / NRSP_B.

Percent change in SCORAD score from Baseline

For each subject, define
SCORAD_pct_chg = (SCORAD_16 – SCORAD_B) *100/SCORAD_B
where
SCORAD_B= SCORAD at Baseline and SCORAD_16 = SCORAD at Week 16.

Change from Baseline in DLQI at Week 16

For each subject, define
DLQI_chg = DLQI_16 – DLQI_B,
where
DLQI_B = DLQI at Baseline and DLQI_16= DLQI at Week 16.

17.2.1. Missing Data Methods for Secondary Efficacy Endpoints

Missing efficacy responses will be handled using the MI procedure described in Section 17.1.1 for

continuous endpoints and for categorical endpoints, the missing data will be included as patients not meeting the defined condition.

17.2.2. Scoring and Missing Data for the Instruments Used for Secondary Endpoints

Instruction provided by each owner/author of each instrument will be used as described below:

SCORAD: The SCORAD index assesses disease extent and evaluates 6 clinical characteristics – erythema, edema/papulation, oozing/crusts, excoriation, lichenification and dryness – each on a scale of 0 to 3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe). SCORAD also assesses subjective symptoms of pruritus and sleep loss with visual analogue scales where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These 3 aspects: extent of disease (A: range 0-102), disease severity (B; range 0-18) and subjective symptoms (C: range 0-20) will be combined using, A/5 + 7*B/2 + C, to give a maximum possible score of 103.4. If a component (A, B, or C) cannot be calculated due missing data in a single question for that component, the missing question(s) for that component will be imputed using MI to calculate the component and total scores. If more than 1 question within a component is missing, then the SCORAD will be set to missing and imputed using MI as described in Section 17.1.1.

DLQI: The DLQI is a 10- item questionnaire, each taking responses 0 to 3, for a maximum of 30 points. If 1 question is unanswered, this is allocated a score of 0 and the DLQI score summed in the usual way, out of 30. If 2 or more questions are unanswered, the questionnaire is set to missing and imputed using MI as described in Section 17.1.1.

NRS: For NRS, if a subject has less than 2 daily diary entries out of the 7 consecutive days prior to the visit, then the average will not be calculated and the NRS (i.e. weekly average peak score for that visit) will be considered missing. Baseline NRS will be calculated from Day -6 to Day 0, unless that time frame includes fewer than 2 entries, in which case the Baseline value will be calculated from the most recent 2 entries prior to Day 0. A Week 1 score will not be calculated because the time frame from Week 0 to Week 1 is less than the 7 days needed to obtain a weekly average.

Missing NRS for that visit will be imputed by carrying forward the NRS from the previous visit.

17.2.3. Analysis of Secondary Efficacy Variables

The secondary efficacy analyses will be performed using the FAS. Continuous endpoints will be analyzed using ANCOVA models (similar to the analysis for the primary endpoint).

For binary endpoints a logistic regression model adjusting for baseline score and including treatment, visit and all first order interaction terms will be used. Odds ratios, 95% CI and *p* value between treatment groups and placebo group will be presented.

17.3. Exploratory Efficacy Endpoints

Absolute change in EASI score from Baseline to Week 16

For each subject,
EASI_chg_16= EASI_16 – EASI_B,
where
EASI_B= EASI at Baseline and EASI_16 = EASI at Week 16.

Percentage change in EASI score from Baseline to Weeks 4, 8, 12, 20, and 24

For each subject, and for weeks j ∈ (4, 8, 12,16, 20, 24),
EASI_j_pct_chg = (EASI_j – EASI_B) *100/EASI_B
where
EASI_B= EASI at Baseline and EASI_j = EASI at Week j.

Percent change in BSA from Baseline to Weeks 4, 8, 12, 16, 20, and 24

For each subject, and for weeks j ∈ (4, 8, 12, 16, 20, 24),
BSA_j_pct_chg = (BSA_j – BSA_B) *100/BSA_B
where
BSA_B= BSA at Baseline and BSA_j = BSA at Week j.

Absolute change in percent BSA from Baseline to Weeks 4, 8, 12, 16, 20, and 24

For each subject, and for weeks j ∈ (4, 8, 12, 16, 20, 24),
BSA_j_chg = (BSA_j – BSA_B)
where
BSA_B= BSA at Baseline and BSA_j = BSA at Week j.

Absolute change from Baseline in ACQ-6 Score at Weeks 4, 8, 12, 16, 20 and 24

For each subject, and for weeks j ∈ (4, 8, 12,16, 20, 24),
ACQ6_j_chg = (ACQ6_j – ACQ6_B)
where
ACQ6_B= ACQ-6 score at Baseline and ACQ6_j = ACQ-6 score at Week j.

Absolute change in SCORAD scores from Baseline to Weeks 4, 8, 12, 16, 20 and 24

For each subject, and for weeks j ∈ (4, 8, 12, 16, 20, 24),
SCORAD_j_chg = SCORAD_j – SCORAD_B
where
SCORAD_B= SCORAD at Baseline and SCORAD_j = SCORAD at Week j.

Absolute change from Baseline in POEM at Weeks 4, 8, 12,16, 20, and 24.

For each subject, and for weeks j ∈ (4, 8, 12, 16, 20, 24),
POEM_j_chg = POEM _j – POEM _B
where
POEM _B= POEM at Baseline and POEM _j = POEM at Week j.

Proportion of subjects with POEM change ≥ the minimal clinically important difference (MCID)

A change in POEM score of at least 3.4 points is considered clinically important.
For each subject,
POEM _MCID_16= 1 if POEM _16 – POEM _B ≥ 3.4, 0 otherwise
where
POEM _B= POEM at Baseline and POEM _16 = POEM at Week 16.
Then P_ POEM _MCID_16 for each treatment group is (Σ POEM _MCID_16)/n.

Proportion of subjects with DLQI change ≥MCID

A change in DLQI score of at least 4 points is considered clinically important.
For each subject,
DLQI_MCID_16= 1 if DLQI_16 –DLQI_B ≥4, 0 otherwise
where
DLQI_B= DLQI at Baseline and DLQI_16 = DLQI at Week 16.
Then P_ DLQI _MCID_16 for each treatment group is (Σ DLQI _MCID_16)/n.

Absolute change in peak weekly averaged NRS for Pruritus score from Baseline

For each subject and for weeks *j=2, …, 24*, define
NRSP_peak_avg= $\left(\sum_{i=1}^{k} Peak\ NRS\ for\ Pruritis\ on\ Day\ i\right)/k$, where
k = number of days NRS for Pruritis score was recorded for week j.
Then
NRSP__peak_Abs_Chg = (NRSP_peak_avg – NRSP_B).

Absolute change in mean weekly averaged NRS for Pruritus score from Baseline

For each subject and for weeks *j=2, …, 24*, define
NRSP_j_avg= $\left(\sum_{i=1}^{k} NRS\ for\ Pruritis\ on\ Day\ i\right)/k$, where
k = number of days NRS for Pruritis score was recorded for week j.
Then
NRSP_Avg = $(\sum_{i=1}^{m} NRSP\_j\_avg)/m$, where m = the number of Weeks measured
and
NRSP_Abs_Avg = (NRSP_Avg – NRSP_B).

Percent change in mean weekly averaged NRS for Pruritus score from Baseline

For each subject and for weeks *j=2, …, 24*, define
NRSP_j_avg= $\left(\sum_{i=1}^{k} NRS\ for\ Pruritis\ on\ Day\ i\right)/k$, where
k = number of days NRS for Pruritis score was recorded for Week j.
Then
NRSP_Avg = $(\sum_{i=1}^{m} NRSP\_j\_avg)/m$, where m = the number of Weeks measured and NRSP_Pct_Avg = (NRSP_ Avg – NRSP_B) * 100 / NRSP_B.

Proportion of subjects with EASI change ≥MCID

A change in EASI score of at least 6.6 points is considered clinically important.
For each subject,
EASI _MCID_16= 1 if EASI _16 – EASI I_B ≥ 6.6, 0 otherwise
where
EASI _B= EASI at Baseline and EASI _16 = EASI at Week 16.
Then P_ EASI _MCID_16 for each treatment group is (Σ EASI _MCID_16)/n.

Proportion of subjects with SCORAD change ≥MCID

A change in SCORAD score of at least 8.7 points is considered clinically important.
For each subject,
SCORAD _MCID_16= 1 if SCORAD _16 – SCORAD_B ≥ 8.7, 0 otherwise
where
SCORAD _B= EASI at Baseline and SCORAD _16 = EASI at Week 16.

17.3.1. Missing Data Methods for Exploratory Efficacy Endpoints

Missing data for exploratory efficacy endpoint will not be imputed.

17.3.2. Scoring and Missing Data for the Instruments Used for Exploratory Endpoints

17.3.2.1. Asthma Control Questionnaire 6

The ACQ-6 contains 6 questions, each scored from 0 to 6. Responses are captured on paper forms and transcribed into the eCRF. The individual responses are averaged to obtain the total score. If 1 or 2 responses are missing, the total score will be calculated as the average of the completed questions. If 3 or more responses are missing, the total score will be set to missing.

17.3.2.2. Scoring Atopic Dermatitis

Missing SCORAD components will be imputed similar as described in Section 17.2.2, but if a component (A, B or C) can not be computed in a single question for that component, then the entire component will be set as missing, in other words MI will not be executed.

17.4. Analysis of Exploratory Endpoints

Continuous endpoints will be analyzed using the ANCOVA model as described for the primary analysis. For the binary endpoints, a logistic regression model adjusting for baseline score (if available).

18.SAFETY ENDPOINTS

All safety data (AEs, SAEs, vital signs, ECGs, ADA, neutralizing antibodies, and clinical laboratory assessments at each specific time points) will be listed and summarized descriptively using the SAF. Number and percentage of AEs will be presented for each treatment group by preferred term and system organ class of the current Medical Dictionary for Regulatory Authorities (MedDRA).

Individual listings of all SAEs and AEs leading to discontinuation from the study drug will be summarized using the current MedDRA. Summaries and listings of data for vital signs, haematology, clinical chemistry and urinalysis laboratory tests, and ECGs will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

18.1. Adverse Events

AEs will be coded using MedDRA Version 22 and above. A TEAE is defined as:

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

A non-TEAE will be defined as any AE that started on or after the date of informed consent and before the administration of study drug.

Adverse events with missing start dates will be considered treatment-emergent. AEs with missing stop dates or with stop dates after the end of the study date will be considered to have been ongoing at the end of the study.

The severity of AEs will be characterized as “mild, moderate, severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activity.
- Missing severity will be assumed to be the worst severity case i.e. ‘severe’; however, in the listing, it will be displayed as missing.

The causal relationship between the study drug and the AE will be characterized as Unrelated, Unlikely, Possible, Probable, and Unknown (unable to judge). Summaries will be presented as “Related” versus “Not Related”. Categories “Unrelated” and “Unlikely” will be mapped to “Not Related”, while the categories “Possible”, “Probable” and “Unknown” will be mapped to

"Related". Missing relationship will be assumed to be the worst severity case (Related) in data summary tables; however, in listings it will be displayed as missing.

A summary of the number and percentage of patients experiencing TEAEs for each treatment group will be provided. If patient has multiple TEAEs by severity and/or multiple relationships with the study drug, worst-case severity and the worst-case relationship to the study drug will used in the summary.

For TEAE by final outcome, if a patient has multiple TEAEs with different outcomes, the worst case will be reported, where 'Fatal' is the worst outcome. For Action Taken with the Drug, a patient can be counted in more than one category.

The following summary tables will be provided by system order class (SOC) and preferred term (PT) for each treatment group and overall:

- Number of patients with at least one TEAE
- Number of patients with at least one serious TEAE
- Number of patients with at least one TEAE by severity
- Number of patients with at least one TEAE by relationship to study drug
- Number of patients with at least one TEAE leading to permanent discontinuation of study drug
- Number of patients with at least one TEAE leading to interruption of study drug
- Number of patients with at least one TEAE leading to patient withdrawal from study
- Number of patients with at least one TEAE leading to death
- Number of patients with non-TEAE
- TEAE occurring in ≥ 5% of subjects in any treatment group

If an AE occurs more than once, the patient will be counted only once per SOC and once per PT within each SOC. If a patient reports a TEAE more than once within a SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries and the worst-case relationship to the study drug will be used in the corresponding relationship summaries.

Percentages will be calculated relative to the total number of patients in the SAF. The summaries will be sorted by descending frequencies of SOC and descending frequencies of PT with in SOC. Listings will be provided for TEAEs, Serious TEAEs, TEAEs leading to discontinuation from study or from study drug, and TEAEs leading to death for the SAF.

18.2. Deaths

Deaths will be listed and summarized as follows:

- Number (%) of subjects who died by TEAE and study period and reasons for death will be summarized for the SAF by treatment received.
- Death in nonrandomized subjects or randomized and not treated subjects.

18.3. Laboratory Evaluations

The laboratory tests mentioned in SOA will be conducted throughout the study under laboratory evaluations. The actual and change from baseline values at scheduled assessments for each laboratory parameter will be summarized using appropriate descriptive statistics by treatment groups and all available visits. Frequency count and percentages will be provided for categorical variables.

The following summaries also will be provided for laboratory data:

- Incidence of abnormal values according to normal range criteria

Shift table for laboratory test parameters from Baseline will be summarized at each visit.

- Percentages will be based on the number of patients in the SAF population with data at Baseline and the visit of interest.

Haematology and clinical chemistry data will be reported in System International (SI) units.

18.4. Electrocardiogram Evaluations

Results from the central ECG Reading Center will be included in the reporting of this study. The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- HR (bpm)
- Normal
- Abnormal, Not Significant (ANS)
- Abnormal, Significant (AS)

Electrocardiogram data will be listed using the actual and change from baseline values for the

above parameters and will be summarized using descriptive statistics (n, mean, SD, median, and range) by treatment groups and all available visits.

The overall assessment of ECG data results (normal/abnormal) will be summarized using frequency and percentages.

- Absolute values for QT and QTcF interval will be classified as:
  - ≥450 msec
  - ≥480 msec
  - ≥500 msec

Since, there are different ranges for QTcF between the males and females, we will summarize the QTcF by gender as defined below:

Absolute values of the QT interval as: Males: 431- 450 msec; Female: 451- 470 msec.

- Abnormal values of the QT interval as: Males: > 450 msec Females: > 470 msec
- Change from Baseline for QT and QTcF interval will be classified as:
  - >30 msec increase from Baseline
  - >60 msec increase from Baseline

A listing of ECG parameters and of the overall assessment will be provided.

18.5. Vital Signs

The following vital signs will be reported for this study:

- Weight (kg)
- Systolic and diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (breaths/min)
- Temperature (^{0}C)

The actual and change from baseline values for the above parameters will be listed and summarized using descriptive statistics (n, mean, SD, median, and range) by treatment groups and all available visits.

18.6. Physical Examination

Physical examination findings as collected in eCRF and associated abnormalities, along with clinical significance will be tabulated and presented in the listings for the SAF.

Baseline values and changes in the physical examination for the following parameters will be listed and summarized by treatment group and by visit using descriptive statistics:

- General appearance
- Head, eyes, ears, nose and throat
- Respiratory system
- Cardiovascular system
- Lymph nodes
- Extremities
- Abdomen
- Peripheral vascular system
- Musculoskeletal system
- Skin (excluding disease state per protocol AD)
- Neurological system
- Urogenital system

The frequency and percentage of patients with normal, abnormal clinically significant (CS), and abnormal not clinically significant (NCS) assessments will be summarized by body system and treatment group at each available visit.

18.7. Immunogenicity

Immunogenicity (ADA) results will be listed, including date/time of administration, results from the screening assay, confirmatory assay, titer, and neutralizing activity (if applicable). The number and frequency of subjects with confirmed ADA response and with confirmed neutralizing ADA response will be summarized by treatment and visit, as well as overall for a given treatment using the SAF. Efficacy results and/or safety results (such as AEs) may be presented by ADA status, as appropriate. If data permits, the correlation between ADA levels and safety and efficacy endpoints may be analyzed.

19.PHARMACOKINETIC ANALYSIS

The PK endpoints for this study are as follows:

- Apparent clearance (CL/F) of etokimab
- Apparent volume of distribution (Vd/F) of etokimab
- Area under the curve (AUC_{τ}) for the first and last dose
- Maximum concentration (C_{max}) for the first and last dose
- t_{max} for the first and last dose
- $t_{1/2}$ for the last dose

Patient listing(s) of PK sampling dates and times and all concentration-time data will be presented for the SAF. Concentrations which will fall outside the prespecified windows will be identified in the listings, for example:

- If sample for Visit 3 occurs outside the protocol-specified window of 3 to 5 days after Visit 2
- If samples scheduled for predose on Visits 2, 5, 6, and 7 are collected more than 1 hour after dosing
- If sample for Visit 8 occurs outside the protocol-specified window of 2 to 13 days after Visit 7

Concentration data of etokimab in serum will be summarized using descriptive statistics for the PK Analysis Set by treatment (dose amount/schedule) and nominal study day, as described in Section 6. Concentration-time data may be summarized by ADA status (confirmed ADA positive versus those without positive ADA response; patients with neutralizing ADAs). Samples collected outside of the above identified windows will be excluded from the concentration summaries. Concentrations below the LLOQ (BLQ) will be treated as zero for calculation of descriptive statistics. If the calculated mean concentration is BLQ, the mean value will be reported as BLQ, and the SD and CV will be reported as not determined (ND). If the calculated minimum, median, or maximum concentration is BLQ, it will be reported as BLQ. Missing data will not be imputed. If 1 or more concentrations at scheduled time points are missing, they will be reported as missing and will be omitted from the calculation of descriptive statistics.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss

Spelling Format

English US

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in this order:

Treatment Group	**For Tables, Listings and Graphs**
ETOKIMAB 20 mg SC Q4W	ETOKIMAB 20 mg SC Q4W
ETOKIMAB 300 mg load + 150 mg SC Q8W	ETOKIMAB 300 mg load + 150 mg SC Q8W
ETOKIMAB 300 mg load + 150 mg SC Q4W	ETOKIMAB 300 mg load + 150 mg SC Q4W
ETOKIMAB 600 mg load + 300 mg SC Q4W	ETOKIMAB 600 mg load + 300 mg SC Q4W
Placebo	Placebo

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (Default)	**Short Name**	**Visit Number**
Screening (Day 0)	Will be presented as	1
Baseline (Day 1)	W0	2
Day 5, Week 1	W1	3
Day 15, Week 2	W2	4
Day 29, Week 4	W4	5
Day 57, Week 8	W8	6
Day 85, Week 12	W12	7
Day 92, Week 13	W13	8
Day 113, Week 16	W16	9
Day 141, Week 20	W20	10
Day 169, Week 24/EOS/ET	EOS/ET	11
Unscheduled	W#,Visit#	

For outputs, visits for PK will be represented as follows and in that order:

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 15/Week 2	4	Anytime 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 92/Week 13	8	Must occur 2 to 13 days after Visit 7 regardless of window. PK can be pulled at any time during the study visit	
Day 113/Week 16	9	Anytime during the study visit	Anytime during the study visit
Day 141/Week 20	10	Anytime during the study visit	Anytime during the study visit
Day 169/Week 24/ EOS/ET	11	Anytime during the study visit	Anytime during the study visit

Listings

All listings will be ordered by the following:

center-subject ID

randomized treatment group (or treatment received if it is a safety output), first by active dose and then by placebo

date (where applicable).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date ≥ study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date ≥ study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date ≥study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date ≥ study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date ≥ study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date ≥study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date ≥ study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date <= end of treatment, assign as concomitant If stop date ≥ study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. SAMPLE SAS CODE

SAS code to impute missing values:

```
/* creating monotone missing pattern */
proc mi data=adqs_trans nimpute=50 seed=1000  out=adqs_mono
noprint;
by treatment;
    var baseline week1 week2 week4 week8 week12 week16;
    mcmc chain=single impute=monotone;
run;

/* imputation */
proc mi data=adqs_mono out=adqs_monoimp nimpute=1 seed=1000;
by _imputation_;
    class  treatment;
    var  treatment baseline week1 week2 week4 week8 week12
week16;
    monotone regression;
run;
```

SAS code for ANCOVA using imputed values:

```
proc mixed data=<data_set_name> method=reml order=data;
     by _imputation visit_;
    class treatment;
    model response = treatment baseline /outp=outp ddfm=kr
residual;
    lsmeans treatment / cl diff;
    ods output lsmeans=lsmeans diffs=diffs;
run;
*Where
response = change from baseline
treatment = treatment group (ETOKIMAB dose and Placebo);
```

SAS code for logistic regression using imputed values:

```
proc genmod data=<data_set_name> desc;
by visit;
```

```
class treatment;
model response=treatment baseline /dist=bin link=logit;
lsmeans treatment/ diff cl exp;
ods output lsmeans=lsmeans diffs=diffs;
     output out=pred_resp reschi=resid;
run;
*Where
response = binary response variable (Responder and Non-
responder)
treatment = treatment groups (ETOKIMAB dose and Placebo)
```

SAS code to pool the results of imputed test results:

```
proc mianalyze data=mi_lsdiff;
               by treatment _treatment;
               modeleffects estimate;
               stderr stderr;
               ods output ParameterEstimates=est;
run;
```