CLINICAL STUDY PROTOCOL

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

Short Title:	Efficacy, Safety, and Pharmacokinetic Profile of ANB020 in Adults with Moderate-to-Severe Atopic Dermatitis
Protocol Number:	ANB020-005
Amendment Number:	Amendment 3
Product:	Etokimab (also known as ANB020)
National Clinical Trial (NCT) Identified Number:	NCT03533751
Study Phase:	2b
EudraCT Number:	2018-000331-27
IND Number:	137426
IND Sponsor:	AnaptysBio, Inc. 10421 Pacific Center Court, Suite 200 San Diego, CA 92121 United States
Version Number:	v.2.0
Protocol Date:	02 Jul 2019

SUMMARY OF CHANGES FROM PREVIOUS VERSION

One global protocol amendment and 3 country-specific amendments have been issued since the original protocol was issued on 19 March 2018 (see below).

Version	Date
Original Protocol	19 March 2018
Global Protocol Amendments:	
Amendment 2	23 October 2018
Country-specific Protocol Amendments:	
Amendment 1 (Czech Republic)	01 August 2018
Amendment 1 (Germany)	31 July 2018
Amendment 1 (UK)	20 June 2018

Refer to Appendix A for Amendment 2 revisions and for all Amendment 1 revisions.

Substantive changes to Amendment 3, a global protocol amendment, are summarized in Table 1.

The overall rationale for this amendment reflects an update in statistical approach to the data analysis for this study. A hierarchical listing according to priority testing procedure will be employed for the primary and secondary endpoints, and thus, the secondary endpoints have been reorganized. Some previously secondary endpoints have become exploratory endpoints, and some previously exploratory endpoints have become secondary endpoints and clarifying time points for analysis have been added to some endpoints. In addition, an interim analysis has been introduced for the analysis of efficacy data at Week 16. The primary efficacy endpoint is the percent change in EASI score from Baseline to Week 16. The interim analysis will be performed once all subjects have completed the Week 16 visit and will comprise all efficacy data collected through Week 16 and all safety data collected as of the date of data cut-off. These updates and others are summarized in Table 1.

Table 1. Summary of Changes for ANB020-005 Protocol Amendment 3

Affected Section(s)	Summary of Revisions Made	Rationale
Entire protocol	Editorial updates made to fix errors, make the document more navigable, and to be consistent with AnaptysBio Style Guide.	Consistency, correctness, and readability
Entire protocol	Removed the term *violation* in regard to protocol deviations. Only the term *deviation* is now used.	Consistency with reporting terminology.
Sponsor Signature Page	Updated statement of Sponsor's compliance and approval of protocol	Consistent with ICH expectations of Sponsor obligations and AnaptysBio use of Common Protocol Template

Affected Section(s)	Summary of Revisions Made	Rationale
Synopsis Section 3	Re-ordered secondary and exploratory endpoints. Added clarifying time points to some endpoints. Added the safety and tolerability endpoints to the synopsis. Added additional endpoints of: • Incidence of treatment-emergent adverse events • Adverse events leading to discontinuation of study drug • Adverse events resulting in death	To align with changes to the statistical analyses
Synopsis	Added sample size and statistical methods sections to the synopsis	Standard synopsis sections to note key statistical considerations.
Section 3	Revised the PK endpoints description for clarity	Increased clarity for SAP
Section 4.4	Revised the definition of the end of study.	Revised for clarity.
Section 6.5.2 Section 7.2 Section 9.5.4	Clarified definition of rescue medication/therapy and how subjects who receive rescue medication are to be handled. Clarified that systemic rescue medication is a reason for withdrawal from treatment.	Increased clarity and instruction for study centers. Defines nonresponders for data analysis.
Section 6.1.2	Updated Tables 3 and 5 to clarify that the 300/150 mg Q8W treatment group receives placebo at doses 2 and 4.	Consistency with protocol body text.
Section 6.4 Section 7.1 Section 7.2	Clarified that subjects who miss 2 consecutive doses after the loading dose will be considered noncompliant with study drug and will be discontinued from the study.	Clarification of study drug compliance
Section 7.2	Clarified that subjects who discontinue for pregnancy should also complete safety follow-up assessments	Accuracy and completeness
Section 8.6.5	Added text that clarifies Medical Monitor actions following an SAE entry into the eCRF.	Clarifies the safety reporting process.
Section 8.6.7	Revised instructions for the treatment of a potential overdose of study treatment	A protocol clarification letter on this subject was issued to study centers on 22 Jan 2019. This change aligns the protocol with the issued clarification letter language.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 9 Section 9.1 Section 9.2 Section 9.4 Section 9.5 Section 9.5.1 Section 9.5.2 Section 9.5.3 Section 9.5.4 Section 9.6 Section 9.6.1 Section 9.6.2 Section 9.6.4 Section 9.6.5	These sections were significantly revised and re-ordered to reflect changes in the approach to statistical analysis for this study. Secondary efficacy endpoints now reflect a hierarchical testing procedure and other sections have been compressed or renamed to reflect the comprehensive update to the statistical analysis for this study.	A hierarchical testing procedure will be employed for the primary and secondary endpoints, and thus, the secondary endpoints have been reorganized. Some previously secondary endpoints have become exploratory endpoints, and some previously exploratory endpoints have become secondary endpoints. Because of the comprehensive nature of the change to the statistical approach, the text of the statistical analysis sections required significant changes.
Section 9.3 (formerly Section 9.2)	Removed the ITT analysis set and revised the definitions of other analysis sets.	Changes to the analysis sets made in conjunction with the changes to the statistical analyses.
Section 9.7 (formerly Section 9.6)	An interim analysis has been added	The interim analysis was added in preparation for dose selection in the Phase 3 study.
Section 9.7.1	This section, formerly titled Tabulation of Individual Participant Data has been deleted.	This standalone section was removed as superfluous and information regarding the tabulation of individual participant data is covered in other sections.
Section 10.1.2	Added text that failure of the investigator to comply with ICH-GCP guidelines and FDA guidelines/regulations may result in early closure of the study center.	Added for completeness and clarity.
Section 10.1.5	Updated Medical Monitor	The Sponsor Medical Monitor for this study has changed, so the protocol has been updated to reflect the new Medical Monitor information.
Section 10.1.6	Updated DSMB information	With the addition of the Week 16 interim analysis, subsets of data review provided to the DSMB are clarified.
Section 10.1.9.2	Clarified that study records should not be destroyed without prior authorization from the Sponsor.	Revised for clarity and completeness.
Section 10.1.10	Added a list of protocol deviations that may affect the primary analysis	The major protocol deviations according to ICH guidelines have been added, any additional deviations will be determined per discussion at the time of data review prior to database lock.
Section 10.4	Removed Section 10.4	Improved information flow.

Affected Section(s)	Summary of Revisions Made	Rationale
Appendices	Moved the Hanifin and Rajka Guidelines from Appendix B to Appendix N	There were previously 2 Appendix B's, this move retains the appendix numbering for the remaining appendices.

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, ICH GCP guidelines) and the protocol.

[redacted]

3 July 2019
Date

AnaptysBio, Inc.

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: 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

PROTOCOL NO: ANB020-005

AMENDMENT NO: Amendment 3

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

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STATEMENT OF COMPLIANCE

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

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

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A 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

Short Title: Efficacy, Safety, and Pharmacokinetic Profile of ANB020 in Adults with Moderate-to-Severe Atopic Dermatitis

Protocol Number: ANB020-005

Study 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 pharmacokinetics (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, treatment period of 16 weeks (Week 0 to 16), and 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 randomized on Day 1 to one of the following 5 treatment arms in a 1:1:1:1:1 ratio:

- Etokimab 20 mg subcutaneous (SC) every 4 weeks (Q4W)
- Etokimab 300 mg load + 150 mg SC Q4W
- Etokimab 300 mg load + 150 mg SC every 8 weeks
- 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) (see Section 1.3).

The subject's disease activity (response to study treatment) will be evaluated using the Eczema Area and Severity Index (EASI), Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD), and Scoring Atopic Dermatitis (SCORAD) assessments. The patient reported outcome measurements (Patient Oriented Eczema Measure [POEM], Asthma Control Questionnaire-6 [ACQ-6], and Dermatology Life Quality Index [DLQI]) will be performed first at visits mentioned in the Schedule of Activities (SOA) (see Section 1.3) before any other study procedures (except informed consent at screening visit). Dermatology Life Quality

Index and POEM questionnaire 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 (based on availability of validated translations in participating countries). The numerical rating scale (NRS) for pruritus, also a patient reported outcome measurement, will be completed daily via an electronic patient reported outcomes (ePRO) 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 (see Section 1.3).

Safety assessments including adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examination, electrocardiograms (ECGs), and laboratory measurements will be performed as specified in SOA (see Section 1.3). A Data Safety Monitoring Board (DSMB) will be instituted to periodically review and evaluate the study data for subject's safety and advise the Sponsor of potential safety signals (see Section 10.1.6).

Objectives:

Primary Objective:

- To evaluate the effects of etokimab on skin lesions

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 (QoL)

Endpoints:

Primary Endpoint:

- Percent change in EASI score from Baseline to Week 16.

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 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 NRS for pruritus score reduction from Baseline of ≥4
- Percent change in peak weekly averaged NRS for pruritus score from Baseline
- Percent change in SCORAD scores from Baseline
- Change from Baseline in DLQI

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 [BP], temperature, respiration rate, heart rate [HR], and weight) • Changes in clinical safety laboratory tests (hematology, chemistry, and urinalysis) • Changes in ECG parameters • Immunogenicity (anti-drug antibody [ADA] and neutralizing ADA)
Study Population:	Approximately 300 adults between the ages of 18 and 75 years of age with clinically diagnosed AD based on Hanifin/Rajka criteria with symptoms present for at least 6 months prior to Baseline. Eligible subjects must also have a body mass index of 18 ≤35 kg/m^2, and an EASI score of ≥16, body surface area (BSA) involvement of ≥10%, and a vIGA-AD score (5-point scale) ≥3 at screening and Baseline.
Phase:	2b
Description of Sites/Facilities Enrolling Participants:	Approximately 83 investigators and study centers across the United States, Canada, and Europe are expected to participate in this study. Approximately 300 subjects will be randomly assigned to study treatment for an estimated total of approximately 60 evaluable subjects per treatment group.
Description of Study Intervention:	Etokimab or matching placebo for SC injection: • Sterile etokimab in single-use glass vials; each vial will contain 100 mg/mL of etokimab • Sterile placebo in single-use glass vials; each vial will contain no active drug product See Figure 1 for dosing regimen.
Study Duration:	Study duration will last approximately 12 months.
Participant Duration:	The study will have a screening period of up to 4 weeks (Weeks -4 to 0), treatment period of 16 weeks (Week 0 to 16), and safety follow-up period of 8 weeks (Week 16 to 24).
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, a total sample of approximately 300 subjects (60 subjects per treatment arm) 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 arm respectively) with a covariate R-squared of 0.300.

Statistical Methods

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the total population for each treatment arm.

The primary endpoint will be assessed using ANCOVA with baseline EASI score as a covariate. Endpoints involving differences in proportion will be assessed using logistic regression with baseline EASI score and treatment type as a covariate.

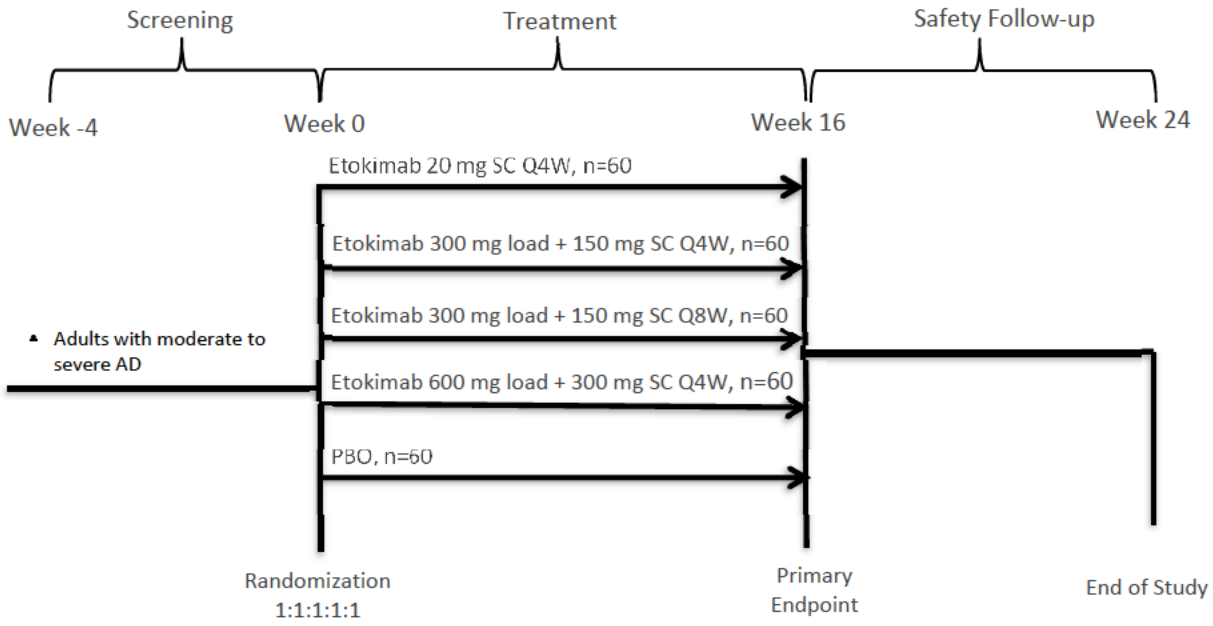
All safety data will be summarized using descriptive statistics.

An Interim Analysis (IA) will be performed when 100% of subjects complete their 16-Week for final assessment of all primary and secondary efficacy endpoints (for Week 16) and all safety data available (up to Week 24). Final database lock will include exploratory efficacy and safety analysis for all subjects for Weeks 20 and 24.

Additional details about the statistical methods including, but not limited, analysis sets, missing data strategies, etc. will be provided in the body of the protocol and the Statistical Analysis Plan (SAP) which will be prepared as a separate document prior to database lock.

1.2 SCHEMA

Figure 1. Study Schema for Protocol ANB020-005



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

1.3 SCHEDULE OF ACTIVITIES (SOA)

Phase	**Screening**	**Treatment**								**Safety Follow-Up**	
Week	**-4 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**13**	**16**	**20**	**24/EOS/ ETV**
Study Day	**-28 to 0**	**1d**	**5± 1d**	**15±2d**	**29±2d**	**57±3d**	**85±3d**	**92±5d**	**113±5d**	**141±5d**	**169±5d**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed consent	X										
Contact IXRS to enroll subject	X	X									
Inclusion/exclusion criteria[a]	X	X									
Medical history (including prior AD therapy)	X										
Height	X										
Physical examination[b]	X	X							X		X
Vital signs, including weight[c]	X	X		X	X	X	X		X	X	X
EASI, vIGA-AD, SCORAD assessments[d]	X	X	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, HIV, hepatitis B and C viral testing, TB testing[h]	X										
Hematology, chemistry[i]	X	X	X		X	X	X		X		X
Urinalysis[j]	X	X							X		X
Pharmacokinetics[k]		X	X	X	X	X	X	X	X	X	X
Immunogenicity[l]		X			X	X	X		X	X	X
NRS for pruritus (daily)[m]	←										→
POEM[n]	X	X	X	X	X	X	X		X	X	X
DLQI[n]		X	X		X	X			X		X
ACQ-6[n, o]		X	X		X	X			X		X

Phase	Screening	Treatment								Safety Follow-Up	
Week	-4 to 0	0	1	2	4	8	12	13	16	20	24/EOS/ ETV
Study Day	-28 to 0	1d	5± 1d	15±2d	29±2d	57±3d	85±3d	92±5d	113±5d	141±5d	169±5d
Visit	1	2	3	4	5	6	7	8	9	10	11
Study drug injection[p]		X			X	X	X				
ePRO device collection[q]	X										X
Adverse event monitoring	←										→
Concomitant therapy[r]	←										→

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; AD = atopic dermatitis; d = days; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOS = end of study; ePRO = electronic patient reported outcomes; ETV = early termination visit; HIV = human immunodeficiency virus; IXRS = interactive web response system; NRS = numeric rating scale; POEM = Patient Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis; TB = tuberculosis; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis.

Footnotes on the next 2 pages.

[a] Inclusion/exclusion criteria based on all screening assessments and non-central laboratory Week 0/Day 1 assessments pre-dose are to be reviewed before enrollment.

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

[c] Vital signs assessments (should be performed before blood sampling and before administration of investigational product at each study visit where administered. Blood pressure should be obtained after at least 5 minutes of rest in a seated position.

[d] Skin efficacy assessments should be performed by a qualified individual, and it is recommended the same Investigator/Sub-investigator completes the scales and questionnaires for all time points for a given subject.

[e] 12-lead electrocardiogram should be performed after 10 minutes of rest in a supine position before the blood sample is collected.

[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. 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 on Week 0, 4, 8, and 12. A negative result must be obtained at all dosing visits before subject may be randomized.

[h] HIV 1 and 2, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody will be assessed. In addition, tuberculosis testing by interferon-gamma (IFN-γ) release assay (IGRA) will be performed on a country-by-country basis if required by regulatory authorities (eg, Czech Republic) or ethics boards.

[i] Hematology and chemistry: Blood samples will be taken prior to dosing.

[j] Urinalysis: Urine samples will be collected prior to dosing at Visit 2 (Day 1) and at any time during Visits 1, 9, and 11.

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

- Visit 2: prior to dosing.
- Visit 3: any time during the visit. Visit 3 must occur 3 to 5 days after Visit 2 regardless of visit window.
- Visit 4: any time during the visit.
- Visits 5, 6, and 7: prior to dosing.
- Visits 8: any time during the visit. Visit 8 must occur 2 to 13 days after Visit 7 regardless of visit window.
- Visits 9, 10, and 11: any time during each visit.

Samples should be obtained prior to administering study drug if an administration coincides with the visit.

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

- Visits 2, 5, 6, and 7: prior to dosing.
- Visits 9, 10, and 11: any time during each visit.

Samples should be obtained prior to administering study drug if an administration coincides with the visit.

[m] Subject will be instructed to perform this assessment daily in their ePRO device. Subject will be retrained as needed to be compliant with these assessments upon review at each visit by staff.

[n] Patient-reported outcome measurements should be done first at mentioned visits before any other study procedures (except informed consent at screening visit).

[o] The ACQ-6 will be assessed only in subjects with an active asthma disease, whose primary language is English (based on availability of validated translations in participating countries).

[p] Subject is required to remain on site for 2 hours post injection at Weeks 0, 4, 8, and 12 for observation.

[q] The ePRO device will be dispensed to the subject at the screening visit with training on login and completion of scales/questions. The subjects should bring ePRO device to each visit. The ePRO device should be returned to the site at the Week 24 (EOS) visit. If the Subject is discontinued from the study for any reason, the ePRO device will be returned to the site within 7 days of subject notification, otherwise the ePRO device will be collected at EOS.

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

2 INTRODUCTION

2.1 STUDY RATIONALE

Current therapy for moderate to severe atopic dermatitis (AD) is limited. Typical treatment modalities include nonsystemic treatment with emollients, topical corticosteroids, topical phosphodiesterase 4 inhibitors, and topical calcineurin inhibitors. The majority of patients achieve disease control with these standard nonsystemic treatments. However, due to disease severity, treatment-related adverse reactions, or other factors, some patients do not achieve adequate disease control. Thus, there is need for long-term therapeutic control in moderate to severe AD. The IL-33 plays an important role in T-helper 2 (Th2)-mediated cellular immunity, and in the pathogenesis of AD.[1,2,3] It functions as a pleiotropic inflammatory cytokine orchestrating a diverse array of cellular immune responses and potently drives production of Th2 cell associated cytokines such as IL-4, IL-5 and IL-13. Monoclonal antibodies (mAbs) targeting such cytokines might represent a novel approach to control AD. Etokimab is a humanized mAb that specifically neutralizes human IL-33, thereby blocking the interaction of IL-33 with the IL-33 receptor, ST2, and subsequently inhibiting IL-33 driven downstream signaling and cellular responses. Targeting IL-33 with etokimab should impact the downstream Th2 cell cytokines involved in AD pathogenesis, and may provide a novel beneficial therapy to subjects with AD. This study is designed to evaluate the efficacy, safety, and pharmacokinetic (PK) profile of etokimab in subjects with moderate to severe AD.

2.2 BACKGROUND

2.2.1 BACKGROUND OF DISEASE

Atopic dermatitis is a common chronic inflammatory skin disease that affects both children and adults with a prevalence of 30% and 10%, respectively.[4] The hallmarks of AD are chronic, relapsing episodes of skin inflammation with disturbance of epidermal barrier function that culminates in dry skin.[5] AD is often associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of Type 1 allergies, allergic rhinitis, or asthma.[6] The etiology of AD is not entirely understood but involves a multiplicity of factors, including skin barrier abnormalities, defects in innate immunity response, Th2-skewed adaptive immune response, and altered skin resident microbial flora. AD is often associated with, or is a prelude to the development of asthma, and other allergic diseases. The combination of these conditions and their interleaved progression has been defined as the atopic march. The interconnectivity among all these conditions, forming the atopic march, suggests that common pathogenic mechanisms are shared amongst all these conditions. In this context, growing evidence indicates that IL-33 is one of the key initiators of this shared pathogenic cascade.

Current therapies for AD have limited efficacy in moderate to severe disease and most are focused on topical treatments such as corticosteroids and calcineurin inhibitors. Majority of the subjects achieve disease control with these standard nonsystemic treatments. However, there is a significant need for new effective systemic therapies for AD that is not controlled with optimal topical therapy. Biologics have been considered for the treatment of subjects with severe AD. Dupilumab, an mAb that blocks the action of the Th2 cytokines, IL-4, and IL-13, has been tested in clinical studies in AD. The results of these clinical studies have indicated that this mAb provided reduction in the signs and symptoms of disease and

led to its approval for the treatment of AD in the United States and European Union. This is encouraging for the development of etokimab, which targets IL-33, upstream of IL-4, IL-13, and other Th2 cytokines. Etokimab would offer an additional treatment approach to this disease where there remains a need for novel effective therapies.

2.2.2 BACKGROUND OF ETOKIMAB

Etokimab has been adopted as the non-proprietary name for ANB020. Therefore, ANB020 will be referred to as etokimab, interchangeably, in this clinical study protocol.

Etokimab is a first-in-class, anti-interleukin-33 therapeutic antibody to treat Th2 cell driven inflammatory diseases with underlying interleukin (IL)-33 dysregulation. Etokimab is a humanized immunoglobulin subtype G1/kappa (IgG1/kappa) mAb that specifically neutralizes the biological effects of human IL-33, a member of the IL-1 superfamily[7] and a multifunctional cytokine that plays an important role in Th2 mediated cellular immunity and in the pathogenesis of atopic diseases.[1,2] Etokimab binds to and inhibits the interaction of IL-33 with its specific cell surface receptor (ST2) thereby blocking IL-33 driven downstream signaling and subsequent cellular responses. It is being developed for the treatment of atopic diseases, such as eosinophilic asthma and chronic rhinosinusitis with nasal polyps.

2.2.2.1 NONCLINICAL STUDIES WITH ETOKIMAB

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

- Etokimab shows reactivity with human and cynomolgus monkey IL-33 (dissociation constant of 1 pM vs 37 pM, respectively), but not with mouse or rat IL-33.
- In primary human and cynomolgus monkey cell populations, in peripheral blood mononuclear cells and human whole blood, etokimab inhibited IL-33 induced interferon gamma (IFN-γ) production. In human basophils, etokimab also inhibited IL-33 induced IL-5 production.
- Etokimab can reduce eosinophilia in mice treated with human IL-33.
- The observed serum apparent terminal half-life ($t_{1/2}$) of etokimab in cynomolgus monkeys was 160 hours after a single intravenous (IV) dose administration, and 187 hours after a single subcutaneous (SC) dose administration at 10 mg/kg, consistent with the anticipated PK characteristics for a human IgG1 scaffold mAb in the monkey.
- A multiple dose, good laboratory practice compliant toxicology and toxicokinetic study (4- and 13-week duration with recovery phase) has been conducted with etokimab administered by SC and intravenous (IV) injection to cynomolgus monkeys. These studies produced no significant test article related effects and established a No Observed Adverse Effect Level of 50 mg/kg, the highest dose tested.

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

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

2.2.2.2 CLINICAL STUDIES WITH ETOKIMAB

Etokimab has been administered to humans in 2 phase 1 healthy volunteer studies (ANB020-001 and ANB020-BA-01) and a phase 2a proof-of-concept study (ANB020-002) in patients with moderate to severe AD. Detailed clinical experience with etokimab is provided in the Etokimab IB.

2.2.2.2.1 STUDY ANB020-001

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

In the SAD cohort, 1 serious adverse event/suspected unexpected severe adverse reaction (SAE/SUSAR) occurred in a subject who was randomly assigned to etokimab (750 mg) as a single IV injection. The subject developed severe neutropenia ([redacted] on Day 22 post-dose. The neutrophils level remained clinically significantly low ([redacted]) on Day 24, but the level returned to normal range by Day 29. The subject reported to have had prodromal viral symptoms prior the neutropenia episode and clear clinical manifestations (adenoapathy) of an ongoing viral infection. This might indicate that concomitant (viral infection) factors could have triggered the neutropenia episode. However, it cannot be formally excluded that IL-33 neutralization might have had a contributing role in the neutropenic episode.

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

6 subjects (83%) following SC injection of etokimab, 13 of 18 subjects (72%) following IV infusion of etokimab, and 6 of 8 subjects (75%) following administration of placebo, with a total of 45 TEAEs.

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

2.2.2.2.2 STUDY ANB020-BA-01

Study (ANB020-BA-01) was a phase 1 study to assessed PK, safety, and tolerability of a single 100 mg SQ or IV dose of etokimab (current new formulation compared to Study ANB020-001) in healthy male and female subjects. The PK results of Study ANB020-BA-01 are consistent with results of Study ANB020-001. Administration of a single dose of etokimab 100 mg SQ injection or IV infusion was safe and well-tolerated in healthy male and female subjects. There were no new or unexpected safety findings compared to Study ANB020-001.

2.2.2.2.3 STUDY ANB020-002

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

All 12 subjects included in the Safety Analysis Set experienced at least 1 TEAE during the study. During the placebo period (from Day 1 to Day 8 prior to etokimab administration), 8 (66.7%) subjects experienced at least 1 TEAE and after administration of etokimab (on Day 8), 11 (91.7%) subjects experienced at least 1 TEAE. A total of 10 (83.3%) subjects experienced at least 1 TEAE considered related to etokimab by the Investigator. Only 1 (8.3%) subject experienced an SAE (exacerbation of pre-existing depression) after etokimab administration of severe intensity and considered to be unrelated to study drug. None of the subjects discontinued the study due to a TEAE. The most commonly reported TEAEs were dizziness and headache (3 subjects [25%] each) followed by upper respiratory tract infection, urinary tract infection, peripheral swelling, cough, and urticaria (2 subjects [16.7%] each).

The mean total Eczema Area and Severity Index (EASI) score decreased statistically significantly after the administration of etokimab. On Day 15, the mean-total EASI score was 19.2-and the mean treatment difference from Baseline in the total EASI score was -10.8. On Day 22 and Day 36, the mean treatment difference from Baseline in the total EASI score was -16.3 (p-value<0.0001) and -17.5 (p-value=0.0008), respectively.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

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

Serum chemistry results were also all in the normal range. A total of 81% subjects in the placebo group and 79% subjects in the etokimab group had at least 1 TEAE during the study. The most commonly reported TEAEs of mild to moderate intensity included upper respiratory tract infection (50% versus 48% in placebo and etokimab group, respectively) and headache (32% versus 27% in placebo and ANB020 group, respectively). Of all the AEs reported across all dose groups, 44% were reported as possible related and 36% were reported as unrelated. One SAE of decreased neutrophils was reported in the 750 mg dose group which resolved prior to the study completion with no sequelae. No other observations of decreased neutrophils were observed. No dose dependent AE presentation was evident.

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

One SAE of hospitalization for depression (exacerbation of pre-existing depression) of severe intensity was reported in Study ANB020-002. A [redacted]r-old [redacted] patient with a moderate to severe AD who experienced the SAE 157 days after receiving a single dose of etokimab 300 mg IV. The event was considered unlikely related to the study drug by the Investigator and Sponsor.

Although there is no evidence to date for an allergic/anaphylactic reaction to etokimab, such a reaction to either the active protein or excipients is possible. Some symptoms of allergic reactions are rash, wheezing or difficulty breathing, dizziness or fainting (also a possible outcome of a drop in BP), swelling around the mouth, throat or eyes, a fast HR, or sweating. Subjects with true allergic/anaphylactic reactions should not receive further doses of the product.

Monoclonal antibodies may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions, but which are mediated through direct release of cytokines or other

pro-inflammatory mediators. Such reactions may be termed infusion-related reactions. Infusion-related reactions typically occur with the first administration of a monoclonal antibody product and are generally less frequent and/or less severe with subsequent doses.

Allergic/anaphylactic reactions and infusion-related reactions typically begin during, or within several hours of dose administration. The onset of symptoms may be rapid, and some reactions may be life threatening. Etokimab should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available.

Resistance to the therapeutic effects of mAbs can occur in rare cases due to development of neutralizing antibodies by the patient's immune system.

Details about specific risks for subjects in this clinical trial can be found in the etokimab IB and informed consent form (ICF).

2.3.2 KNOWN POTENTIAL BENEFITS

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

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

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To evaluate the effects of etokimab on skin lesions	• Percent change in EASI score from Baseline to Week 16	Percent change in EASI score is an outcome measure that has been established as clinically relevant for assessing treatment response in atopic dermatitis
Secondary Efficacy Endpoints		
• To evaluate the safety and tolerability of etokimab • To evaluate the effects of etokimab on pruritus symptoms • To evaluate the effects of etokimab on QoL	The secondary 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 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 NRS for pruritus score reduction from Baseline of ≥4 • Percent change in peak weekly averaged NRS for pruritus score from Baseline • Percent change in Scoring Atopic Dermatitis (SCORAD) scores from Baseline to • Change from Baseline in Dermatology Life Quality Index (DLQI)	These endpoints are outcome measures that have been established as clinically relevant for assessing treatment response to mAbs for the management of signs and symptoms in patients with atopic dermatitis

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Exploratory Endpoints		
• To evaluate the immunogenicity of etokimab • To characterize the PK of etokimab • To evaluate the effects of etokimab on asthma symptoms	The exploratory endpoints at Week 16 and other clinical assessment time points, unless otherwise indicated: • Absolute change in EASI score from Baseline to Week 16 • Percentage change in EASI score from Baseline to Weeks 4, 8, 16, 20, and 24 • Percent change in body surface area (BSA) from Baseline to Weeks 4, 8, 16, 20, and 24 • Absolute change in percent BSA from Baseline to Weeks 4, 8, 16, 20, and 24 • Change from Baseline in ACQ-6 Score at Weeks 4, 8, 16, and 24 • Absolute change in SCORAD scores from Baseline to Weeks 4, 8, 16, and 24 • Change from Baseline in POEM at Weeks 4, 8, 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	These additional measures of treatment response are established methods to characterize the clinical impact of treatment Patient-reported outcomes specific to AD provide additional evidence to support the physician assessment of outcome

ACQ-6 = Asthma Control Questionnaire -6; BSA = body surface area; EASI = Eczema Area Severity Index; mAbs = monoclonal antibodies; MCID = minimal clinically important difference; NRS = numerical rating scale; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis; vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis.

Safety and Tolerability Endpoints:

The safety and tolerability endpoints of this study are as follows:

- Incidence of AEs.
- Incidence of SAEs
- Incidence of TEAEs
- AEs leading to discontinuation of study drug
- AEs leading to withdrawal from the study
- AEs resulting in death
- Changes in vital signs (BP, temperature, respiration rate, HR, and weight).
- Changes in clinical safety laboratory tests (hematology, chemistry, and urinalysis).
- Changes in ECG parameters.
- Immunogenicity (anti-drug antibody [ADA] and neutralizing ADA).

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 SC administration. PK 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 STUDY DESIGN

4.1 OVERALL DESIGN

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 etokimab compared to placebo in adult subjects with moderate to severe 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, treatment period of 16 weeks (Week 0 to 16) and 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 randomized on Day 1 to one of the following 5 treatment arms in a 1:1:1:1:1 ratio.

- 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) (see Section 1.3).

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 specified in the Schedule of Activities (SOA;see Section 1.3) before any other study procedures (except informed consent at 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 who can read and understand English. The NRS (numerical rating scale) for pruritus , also a patient reported outcome, will be completed daily via electronic patient reported outcome (ePRO) 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 (see Section 1.3).

Safety assessments including AE/SAE monitoring, vital signs, physical examination, ECGs, and laboratory measurements will be performed as specified in SOA (see Section 1.3). A Data Safety Monitoring Board will be instituted to periodically review and evaluate the study data for subject's safety and advise the Sponsor of potential safety signals.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Etokimab, is a first-in-class, anti-IL-33 therapeutic antibody developed to treat Th2 cell driven inflammatory diseases with underlying IL-33 dysregulation. Preliminary evidence of this compound's significant pharmacodynamic (PD) activity in terms of cytokine modulation has been demonstrated in nonclinical and clinical studies, justifying its further development in subjects with AD. Subjects with moderate to severe AD often have inadequate disease control from currently available topical treatments and uncontrolled AD significantly affects their quality of life. Systemic immunomodulatory therapy including oral corticosteroids has been used to treat these subjects but have significant side effects. The use of more targeted immune modulators such as etokimab may reduce the Th2 specific inflammation

triggering disease with fewer side effects. Other monoclonal Th2 immune modulators such as dupilumab have shown promising results in clinical studies.

This study is a dose-ranging study aiming to assess the effects of etokimab compared to placebo in subjects with AD and provide evidence of a desired short-term clinical outcome. This study will use a placebo arm to allow for comparative efficacy assessments. Most of the subjects will be randomized to an active treatment arm. The $t_{1/2}$ of etokimab was approximately 2 weeks in phase 1 studies in healthy subjects. Following subjects for 8 weeks after the last etokimab administration will allow time for additional PK, and safety assessments.

4.3 JUSTIFICATION FOR DOSE

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

4.4 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all scheduled study visits, including the last visit on Day 169 (see Section 1.3) or the last scheduled assessment (see Section 6.7).

The study is considered completed at the time the last subject has undergone all procedures associated with the last visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male or female subjects must be 18 to 75 years of age, at the time of signing the informed consent.
2. Body mass index (BMI) of 18 to ≤35 kg/m^2 at screening.
3. Clinically confirmed diagnosis of AD based on the Hanifin/Rajka criteria (see Appendix N) with symptoms present for at least 6 months prior to Baseline.

4. Eczema Area and Severity Index (EASI) score ≥16, BSA involvement ≥10%, and a vIGA-AD score (5-point scale) ≥3 at screening and Baseline.

5. Subjects with a history (within 1 year prior to screening) of 1 or more of the following:

   a. Inadequate response to topical treatment,
   b. Use of systemic treatments to treat AD, and/or
   c. For whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).

6. Has continued daily routine of applying non-medicated emollient (moisturizer) without any changes for a period of at least 7 days prior to Baseline.

7. Contraception and pregnancy:

   a. A male subject must agree to use contraception as detailed in Appendix C of this 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 must have a negative serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test at Baseline (see Appendix C), is not lactating, and at least one of the following conditions applies:

      i. Not a woman of childbearing potential (WOCBP) as defined in Appendix C OR

      ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix C during the treatment period and for at least 3 months after receiving the last dose of study treatment and refrain from donating oocytes (eggs) during this period. The female subject's selected form of contraception must be effective by the time the female subject enters into the study (eg, hormonal contraception should be initiated at least 28 days before Day 1).

8. Capable of giving signed informed consent and understanding the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

1. Treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), or crisaborole within 2 weeks before dosing (Day 1), or, in the opinion of the Investigator, likely to require such treatment(s) during the first 2 weeks of study treatment.

2. History of prior exposure to an anti-IL-33 antibody.

3. Exposure to an investigational or licensed or other anti Th2 type cytokine or cytokine receptor antagonist (eg, IL-4, IL-5, IL-13, IL-31, ST2, and thymic stromal lymphopoietin [TSLP]) within 16 weeks or 5 half-lives before screening, whichever is longer.

4. History of prior exposure to any investigational or biologic systemic treatment within 5 half-lives before screening or is currently enrolled in another clinical study.

5. Have received systemic treatment (including systemic corticosteroids, immunosuppressants or immunomodulating drugs, or phototherapy or use of a tanning booth) within 4 weeks before screening.

6. Treatment with a live vaccine within 4 weeks before screening through Day 1.

7. History of hypersensitivity or allergic reactions to polysorbate 80 a component of etokimab formulation or the inactive ingredients (excipients).

8. History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.

9. History of parasitic infections within 12 months before screening.

10. Have concomitant dermatological (eg, psoriasis, scabies, seborrheic dermatitis, contact dermatitis (irritant or allergic), congenital ichthyoses, cutaneous T-cell lymphoma, photosensitivity dermatoses, immune deficiency diseases, erythroderma of other causes etc.) or medical condition(s) which may interfere with the Investigator's ability to evaluate the subject's response to the study drug from an efficacy or safety perspective.

11. Bacterial infections of the skin which requires hospital admission within 4 weeks before screening through Day 1.

12. Any acute or chronic infection requiring systemic antibiotics, antivirals, or antifungals (IV or oral) within 2 weeks before screening or topical within 1 week before screening.

13. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen or core antibody, or human immunodeficiency virus (HIV) 1 or 2 antibodies.

14. Immunodeficiency disorders (eg, IgA deficiency) or known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, active or latent tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocytosis, aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per Investigator's judgement. NOTE: Suspected active or latent tuberculosis will be based on medical history, physical examination, and standard of care diagnostic methods. Subjects with a positive interferon-gamma (IFN-γ) release assay (IGRA) at screening are not eligible for this study.

15. History of malignancy within 5 years before screening, except completely treated in situ carcinoma of the cervix or treated and non-metastatic squamous or basal cell carcinoma of the skin.

16. Laboratory findings at screening:

    a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN).

    b) Hemoglobin is <11 g/dL.

    c) Neutrophils $<1.5 \times 10^3/\mu L$.

    d) Platelets $<150 \times 10^3/\mu L$.

17. 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.

18. Have any other physical, mental, or medical conditions which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle restrictions are required.

5.4 SCREEN FAILURES

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

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened once.

Examples of rescreening:

- A subject who needs to be treated with rescue medications during screening that is a topical steroid. The subject may be rescreened after resolution of the exacerbation that prompted treatment and after 14 days of completing treatment with TCS, TCI, and/or crisaborole.
- Subjects who do not meet Inclusion criteria “Has continued daily routine of applying nonmedicated emollient (moisturizer) without any changes for a period of 7 days up to Baseline.”
- Subjects who would continue use of antihistamines, or moisturizers containing additives or filaggrin breakdown products that were not initiated 2 weeks prior to the screening visit. They may be rescreened after they have been on a stable antihistamine regimen and/or moisturizer for 2 weeks.
- Any further queries for rescreening must be discussed with the Medical Monitor and approved by the Sponsor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention plan for this study will be provided in a separate document.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Etokimab, is a humanized IgG1/kappa mAb that specifically neutralizes mAb hIL-33. It was selected from a panel of mouse mAb humanized by complementarity determining region grafting, optimized and matured via mammalian cell display and somatic hyper mutation using AnaptysBio's (SHM) XEL™ system to achieve a desired functional inhibitory potency.

Placebo contains no active ingredient and will be similar to etokimab in appearance.

6.1.2 DOSING AND ADMINISTRATION

All eligible subjects will be randomized on Day 1 to 1 of 5 treatment arms, ie, placebo or 1 of the treatment arms dosed with etokimab in a 1:1:1:1:1 ratio followed by remaining study drug dose administration on Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

The dosing details are presented in Table 2, Table 3, Table 4, and Table 5.

Table 2 Dosing Details for Week 0 (Dose 1)

				Etokimab 100 mg/mL solution in 1.2 mL vials			
Dosing Arm	**Dose 1 Week 0**	**Total injections #**	**Total injection Volume**	**Injection 1[a]**	**Injection 2[a]**	**Injection 3[a]**	**Injection 4[a]**
20 mg Q4W	20 mg	4	6 mL	**0.2 mL etokimab** + 1.3 mL placebo = 1.5 mL	1.5 mL placebo	1.5 mL placebo	1.5 mL placebo
300/150 mg Q4W	300 mg	4	6 mL	**1.5 mL etokimab**	**1.5 mL etokimab**	1.5 mL placebo	1.5 mL placebo
300/150 mg Q8W	300 mg	4	6 mL	**1.5 mL etokimab**	**1.5 mL etokimab**	1.5 mL placebo	1.5 mL placebo
600/300 mg Q4W	600 mg	4	6 mL	**1.5 mL etokimab**	**1.5 mL etokimab**	**1.5 mL etokimab**	**1.5 mL etokimab**
Placebo Q4W	Placebo	4	6 mL	1.5 mL placebo	1.5 mL placebo	1.5 mL placebo	1.5 mL placebo

[a] The numbering of injections in this table does not correspond to the order in which the injections will be administered. These will be prepared by an unblinded pharmacist or designee (examples include a state/country approved physician, registered nurse, etc.) and administered by blinded site staff.

Table 3 Dosing Details for Week 4 (Dose 2)

				Etokimab 100 mg/mL solution in 1.2 mL vials	
Dosing Arm	**Dose 2 Week 4**	**Total injections #**	**Total injection Volume**	**Injection 1[a]**	**Injection 2[a]**
20 mg Q4W	20 mg	2	3 mL	**0.2 mL etokimab** + 1.3 mL placebo = 1.5 mL	1.5 mL placebo
300/150 mg Q4W	150 mg	2	3 mL	**1.5 mL etokimab**	1.5 mL placebo
300/150 mg Q8W[b]	Placebo	2	3 mL	1.5 mL placebo	1.5 mL placebo
600/300 mg Q4W	300 mg	2	3 mL	**1.5 mL etokimab**	**1.5 mL etokimab**
Placebo Q4W	Placebo	2	3 mL	1.5 mL placebo	1.5 mL placebo

[a] The numbering of injections in this table does not correspond to the order in which the injections will be administered. These will be prepared by an unblinded pharmacist or designee (examples include a state/country approved physician, registered nurse, etc.) and administered by blinded site staff.

[b] At Week 4, the 300/150 mg Q8W dosing arm will receive a placebo dose. No etokimab will be administered at this visit.

Table 4 Dosing Details for Week 8 (Dose 3)

				Etokimab 100 mg/mL solution in 1.2 mL vials	
Dosing Arm	**Dose 3 Week 8**	**Total injections #**	**Total injection Volume**	**Injection 1[a]**	**Injection 2[a]**
20 mg Q4W	20 mg	2	3 mL	**0.2 mL etokimab** + 1.3 mL placebo = 1.5 mL	1.5 mL placebo
300/150 mg Q4W	150 mg	2	3 mL	**1.5 mL etokimab**	1.5 mL placebo
300/150 mg Q8W	150 mg	2	3 mL	**1.5 mL etokimab**	1.5 mL placebo
600/300 mg Q4W	300 mg	2	3 mL	**1.5 mL etokimab**	**1.5 mL etokimab**
Placebo Q4W	Placebo	2	3 mL	1.5 mL placebo	1.5 mL placebo

[a] The numbering of injections in this table does not correspond to the order in which the injections will be administered. These will be prepared by an unblinded pharmacist or designee (examples include a state/country approved physician, registered nurse, etc.) and administered by blinded site staff.

Table 5 Dosing Details for Week 12 (Dose 4)

				Etokimab 100 mg/mL solution in 1.2 mL vials	
Dosing Arm	**Dose 4 Week 12**	**Total injections #**	**Total injection Volume**	**Injection 1[a]**	**Injection 2[a]**
20 mg Q4W	20 mg	2	3 mL	**0.2 mL etokimab** + 1.3 mL Placebo = 1.5 mL	1.5 mL placebo
300/150 mg Q4W	150 mg	2	3 mL	**1.5 mL etokimab**	1.5 mL placebo
300/150 mg Q8W[b]	Placebo	2	3 mL	1.5 mL placebo	1.5 mL placebo
600/300 mg Q4W	300 mg	2	3 mL	**1.5 mL etokimab**	**1.5 mL etokimab**
Placebo Q4W	Placebo	2	3 mL	1.5 mL placebo	1.5 mL placebo

[a] The numbering of injections in this table does not correspond to the order in which the injections will be administered. These will be prepared by an unblinded pharmacist or designee (examples include a state/country approved physician, registered nurse, etc.) and administered by blinded site staff.

[b] At Week 12, the 300/150 Q8W dosing arm will receive a placebo dose. No etokimab will be administered at this visit.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

Drug accountability forms must be available for inspection at any time.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Etokimab is a sterile, white to slightly opalescent solution that is formulated at 100 mg/mL in 30 mM histidine, 240 mM proline, and 0.01% polysorbate 80 at pH 6.0. Each single-use vial contains 1.2 mL of solution.

Placebo is formulated as a sterile solution of 30 mM histidine, 240 mM proline, and 0.01% polysorbate 80 at pH 6.0. Each single use glass vial contains 1.2 mL of solution.

All investigational product vials will be packaged and labeled as required per country requirements.

6.2.3 PRODUCT STORAGE AND STABILITY

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The etokimab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. Etokimab vials may be stored at room temperature (>8°C to 25°C [46°F to 77°F]) for up to 8 hours. Once etokimab has been diluted with placebo, the solution may be stored at room temperature (>8°C to 25°C [46°F to 77°F]) for up to 8 hours. Etokimab may be stored at room temperature in the undiluted and/or diluted state for a maximum of 8 hours. Vials are intended for single-use only; therefore, any remaining solution should be discarded.

6.2.4 PREPARATION

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

6.2.5 DOSING INSTRUCTIONS

Study drug (etokimab and placebo) will be administered by SC route at 1.5 mL per injection. Etokimab will be administered by SC route at 100 mg/mL concentration:

- Study drug (etokimab and placebo) should be prepared by drawing up the required dosing volume into suitable sized syringe and attaching a dosing needle.
- Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms, so that the same site is not injected for 2 consecutive months.
- To allow for adequate assessment of possible injection site reactions, study drug should be administered only into areas of normal looking skin; injections should be at least 2 inches (5 cm) apart.
- The loading dose should be administered into at least two different locations (eg, different quadrants of the abdomen) to avoid administration of more than 2 injections into the same location.
- Subcutaneous injections should not be given into moles, scars, tattoos or areas where the skin is tender, bruised, red, hard, or not intact.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 RANDOMIZATION

This is a randomized, double blind, placebo-controlled study with limited access to the randomization code. All subjects will be centrally assigned to randomized study treatment using an Interactive Web Response System (IXRS). As subjects become eligible they will be assigned sequential randomization numbers which will be used to assign the allocated treatment based on a randomization schedule. Before the study is initiated, the log in information and directions for the IXRS will be provided to each study center. Study treatment will be prepared and dispensed at the study visits by an unblinded pharmacist or designee as summarized in Section 6.1 and the Pharmacy Manual; the visits at which this will occur are summarized in Section 1.3. Returned study treatment should not be re dispensed to the subjects.

Eligible subjects will be randomized on Day 1 to one of the 5 treatment arms, ie, placebo or one of the treatment arms dosed with etokimab in a 1:1:1:1:1 ratio. Etokimab and placebo will be identical in physical appearance. The Sponsor, Investigator, site staff, and subjects will be blinded to treatment assignment and only the unblinded pharmacist or designee (examples include a state/country approved physician, registered nurse, etc.) will be aware of treatment assignment (etokimab or placebo). The IXRS will be responsible for providing the randomization number to the unblinded pharmacist or designee. The treatment codes will be held by the Sponsor's designated vendor.

6.3.2 BLINDING

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

All entries 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.

6.4 STUDY INTERVENTION COMPLIANCE

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

Subjects who miss 2 consecutive doses after the loading dose will be considered noncompliant and will be discontinued from the study. Missing the loading dose will also result in discontinuation from the study.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications is provided in Appendix D.

6.5.1 ALLOWED MEDICATIONS

Treatment with concomitant therapies for AD during the study is permitted only as outlined in the inclusion criteria (see Section 5.1)/exclusion criteria (see Section 5.2) and as described below. Subjects taking permitted medications should be on stable doses at the baseline visit (Week 0, Day 1) as specified in Section 5.2.

- Throughout the treatment period, subjects will continue to apply their daily routine emollient without any changes at least once daily to all dry areas.
- Women of childbearing potential are to continue using a highly effective form of contraception throughout the study.
- Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted.

The Investigator must record the use of all concomitant medications, both prescribed and over the counter, into the eCRF and subject's medical records. This includes medications used on both a regular and an as needed basis. Subjects should be discouraged from starting any new medication, both prescribed and over the counter, without consulting the Investigator, unless the new medication is required for emergency use or has been prescribed for clinical need. If there is any question whether a medication may be used during the study the site should contact the Medical Monitor.

A list of excluded medications/therapy is provided in Appendix D.

6.5.2 RESCUE MEDICINE

The use of topical and systemic corticosteroids, immunosuppressant/immunomodulating treatments and phototherapy or use of a tanning booth are prohibited during the course of the study (Table 13). If any of these medications are needed to control intolerable AD symptoms, they may be given/utilized at the discretion of the Investigator and will be considered rescue medication/therapy. The Sponsor will not supply any rescue medication or support the cost of rescue therapy.

Subjects who receive any exclusionary topical rescue treatment for more than 2 consecutive days, or for more than 3 days within two consecutive weeks, or for more than 6 days during the treatment period will be considered nonresponders; however, they are allowed to continue study treatment. Subjects who receive phototherapy rescue treatment or utilize tanning booths will be considered nonresponders, but will be allowed to continue study treatment. However, if a subject receives systemic rescue treatment, study treatment is to be immediately discontinued.

All subjects who receive rescue medication/therapy should complete the study assessments according to Section 1.3 whether or not they continue study treatment.

The date and time of any rescue medication administration or treatment, as well as the name and dosage regimen of the rescue medication or treatment, must be recorded.

Anti-inflammatory topical rescue therapy should be administered to lesional skin only. The choice of the corticosteroid should be based upon standard of care considerations (eg, body area involved, severity of skin inflammation). A list of representative topical corticosteroids is provided in Appendix E. Low potency corticosteroids (Class 6/7) cream or ointment are suggested. For more severe inflammation, moderate potency corticosteroids (Class 4/5) are suggested. Topical calcineurin inhibitors (eg, tacrolimus 0.1%) may be an alternative to TCS, in particular, for the treatment of the face, neck, and skin folds.

6.6 DOSE MODIFICATION

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

6.7 TREATMENT AFTER THE END OF THE STUDY

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

30 days after the EOS visit should be reported to the IQVIA Lifecycle Safety team and followed up until it has a resolved or stable outcome or subject is lost to follow-up.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

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

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

In case of early withdrawal from the study or if the subject has missed 2 consecutive doses following the Day 1 loading dose, the subject will be required to return to the study center for an ETV. Procedures should be completed in accordance with the SOA (see Section 1.3) Week 24/ETV.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The subject can be discontinued or withdrawn from study due to following reasons:

- A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety (eg, occurrence of an AE or SAE or a protocol deviation), lack of efficacy, behavioral, lack of compliance, or administrative reasons. Prior to study drug administration, the Investigator decides that the subject should be withdrawn or is at risk. If this decision is made because of an AE or a clinically significant laboratory value, the study drug should not be administered, and appropriate measures are to be taken. AnaptysBio Inc. and/or IQVIA is to be notified immediately.
- Lost to follow-up.
- An anaphylactic or other serious allergic reaction.
- Occurrences of emergency unblinding.
- Use of any excluded/prohibited medications (see Appendix D) that in the opinion of the Investigator or Sponsor necessitates the subject being withdrawn.
- Laboratory abnormalities:
  - ALT or AST >5 times ULN for more than 2 weeks.
  - ALT or AST >3 times ULN AND bilirubin >2 times ULN (total bilirubin >4 times ULN in case of documented Gilbert's syndrome).
- Use of systemic rescue medication. Patients should be withdrawn from treatment, but not necessarily from the study (see Section 6.5.2).

- Termination of the study by the Investigator or Sponsor.
- Pregnancy (see Appendix C and Section 8.2.5).
- Noncompliance with study treatment (Section 6.4)

Any subject who have received at least 1 dose of the study drug, should complete the ETV assessments and return for the safety follow-up assessments.

If a subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

In subjects who are discontinued for pregnancy, after completing ETV assessments and safety follow-up, they should be followed up until outcome of the pregnancy is known (see Section 8.2.5 and Appendix C).

See SOA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects may be replaced in certain circumstances (eg, limited exposure to study drug). The final decision for replacement of subjects will be done on a case by case basis in consultation with Medical Monitor at the Sponsor's designated contract research organization and/or with the Sponsor's Medical Director.

7.3 LOST TO FOLLOW-UP

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

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

- The study center personnel must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. If the re-scheduled visit falls within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned. Missed visits must be captured in the eCRFs and will be recorded as a protocol deviation.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their scheduling are summarized in the Schedule of Activities (see Section 1.3). The study assessment details are presented below:

- Assessments scheduled on the day of study treatment administration must be performed prior to the study treatment injection unless otherwise noted (see Section 1.3).
- There are visits where the protocol requires more than 1 procedure to be completed at the same time point. When indicated, the procedure must follow specific order of events, see Section 1.3 for instructions.
- Immediate safety concerns should be discussed with the Sponsor/designee immediately upon occurrence or awareness to determine if the subject should continue or discontinue in the study.
- Adherence to the study design requirements, including those specified in Section 1.3, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable and the log will be sent weekly to clinical lead.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, is approximately 126 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Severity of AD from Baseline through EOS follow-up will be assessed by the Investigator and/or the subject using the EASI, vIGA-AD, SCORAD, DLQI, POEM, and NRS for Pruritus. In addition, the ACQ-6 will be obtained in subjects with a history of asthma at Baseline.

It is recommended that the same Investigator/Sub-investigator completes the scales and questionnaires for all time points for a given subject. Patient reported outcome assessments (ie, SCORAD, DLQI, POEM, and ACQ-6) should be obtained prior to any other assessments at each visit as per Section 1.3, except for signing of the ICF.

8.1.1 ECZEMA AREA AND SEVERITY INDEX (EASI)

The EASI is an Investigator assessment measuring the severity of clinical signs in AD. The EASI is considered one of the best validated outcome measures for AD. The EASI score assesses the severity and extent of erythema; induration, papulation, and edema; excoriations; and lichenification. The EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD[7, 8]. The EASI score will be recorded at the time points indicated in the SOA (see Section 1.3). The EASI will be captured in electronic clinical outcome assessment (eCOA) tablet. The EASI instructions and forms are in Appendix F.

8.1.2 VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS (VIGA-AD™)

The vIGA-AD is a static 5-point scale to evaluate AD disease severity globally and is frequently assessed in clinical studies. Investigator's vIGA-AD responses will be captured in eCOA tablet. The vIGA-AD result will be recorded at the time points indicated in the Section 1.3. The vIGA-AD scale to be used is in Appendix G.

8.1.3 SEVERITY SCORING OF ATOPIC DERMATITIS (SCORAD)

The SCORAD index, a validated assessment of AD, was developed to standardize the evaluation of the extent and severity of AD. There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject on a visual analog scale, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation.

The SCORAD score is calculated as: A/5 + 7B/2 + C (see Appendix H for more information). Subjects will undergo this assessment at time points specified in Section 1.3. The SCORAD will be captured in eCOA tablet.

8.1.4 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The DLQI is a 10-item, validated questionnaire used in clinical trials to assess the impact of AD disease symptoms and treatment on quality of life. The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess quality of life (QoL) over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QoL.[11] The questionnaire 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 subject should complete the DLQI in Appendix I at the time points indicated in the SOA (see Section 1.3). The DLQI will be captured in eCOA tablet.

8.1.5 PATIENT ORIENTED ECZEMA MEASURE (POEM)

The POEM is a 7-item, validated questionnaire used in clinical trials to assess the severity of eczema as experienced by the subject. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity[12]. The questionnaire 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 subject should complete the POEM at the time points indicated in the SOA (see Section 1.3). The POEM will be captured in eCOA tablet. The subject should complete the POEM questionnaire (see Appendix J).

8.1.6 NUMERICAL RATING SCALE FOR PRURITUS

The NRS for Pruritus is a simple assessment tool that subjects will use to report the intensity of their pruritus (itch) during a daily recall period using an ePRO device. Subjects will be asked 2 questions:

- For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst imaginable itch', how would you rate your itch overall (on average) during the previous 24 hours?"
- For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst imaginable itch', how would you rate your itch at the worst moment during the previous 24 hours?"

The subject should complete the NRS for each of the 2 questions at the time points indicated in the SOA (see Section 1.3). Subjects will be instructed on using ePRO device to record their NRS score. Subjects will complete the rating scale daily through the last study visit. Study center will receive alerts when subjects do not complete the NRS items. Study center will be expected to contact subjects who have missed two consecutive entries to encourage compliance. The NRS for Pruritus will be captured on ePRO handheld device.

8.1.7 ASTHMA CONTROL QUESTIONNAIRE-6

The ACQ-6 will be used in this study to assess the asthma symptoms (night time waking, symptom on waking, activity limitation, and shortness of breath, wheezing, and short acting β agonist [SABA] usage) in subjects with active asthma disease. Subject will be asked to recall their experiences during the previous week by responding to 5 symptom related questions and 1 question related to bronchodilator use. Questions will be scored from 0 (totally controlled) to 6 (severely uncontrolled). The questionnaire will be administered only in subjects with active asthma disease whose primary language is English (based on availability of validated translations in participating countries). The subject should complete the ACQ-6 (see Appendix K) at the time points indicated in the SOA (see Section 1.3). The ACQ-6 responses will be captured by subjects on paper and transcribed into the eCRF.

8.1.8 BODY SURFACE AREA

The BSA affected by AD will be assessed for each major section of the body including the head, trunk, upper extremities, and lower extremities and will be reported as the added total of percentage of all major body sections combined. The subject's BSA will be assessed in Part A of SCORAD assessment.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SOA (see Section 1.3).

Unscheduled safety assessments may be performed at any time during the study.

8.2.1 PHYSICAL EXAMINATIONS

Complete physical examinations will be performed at the time points specified in the SOA (see Section 1.3).

- A complete physical examination includes assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system; extremities; eyes (inspection and vision control); nose; throat; and

neurologic status and will be performed only at screening. All other physical examinations should be abbreviated examinations and address associated complaints or findings, and any other assessments required to evaluate adverse events.

- A detailed examination of the skin should be performed at the time points specified in the SOA (see Section 1.3) for the efficacy assessments (eg, EASI, vIGA-AD, SCORAD).
- Height (in inches) will be measured only at the Screening visit.

8.2.2 VITAL SIGNS

Vital signs will be performed at the time points specified in the SOA (see Section 1.3).

- Body temperature, HR, BP, respiratory rate, and weight will be assessed and entered in eCRF.
- Weight will be measured at time points specified in Schedule of Activities (see Section 1.3).
- NOTE: Body mass index will be calculated automatically using formula BMI=weight (kg)/(height[m^2]) as specified in specified in the SOA (see Section 1.3).
- Blood pressure and pulse rate measurements will be assessed in the seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate measurements should be preceded by approximately 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones etc.).

8.2.3 12-LEAD ECG

A single 12-lead ECG will be obtained at the time points specified in SOA (see Section 1.3).

- 12-lead ECG will be obtained using a validated ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTcF intervals.
- The ECG will be reviewed by the central laboratory team and the instructions and guidelines for collection (eg, equipment), transmission, and archiving of ECG data will be provided in the ECG Manual.
- The ECG will be reviewed by the Investigator or an authorized representative who is experienced in the evaluation of ECGs and assessed for clinical significance.

8.2.4 CLINICAL LABORATORY DATA

Clinical safety laboratory assessments will be performed as below:

- See Appendix B for the list of clinical laboratory tests to be performed and the SOA (see Section 1.3) for the timing and frequency of the tests.
- A central laboratory will be used to perform all laboratory tests, except urine pregnancy dipstick test, which will be assessed by the site staff. However, local laboratory tests will be allowed if the central laboratory results will not be available immediately because the Investigator will need to make an immediate decision for any safety concerns based on laboratory results.
- The Investigator must review the laboratory report, document this review with date of review and their initials/signature, and record any clinically relevant changes occurring during the study in

the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study including the subject's last EOS visit should be repeated until the values return to normal or Baseline or are no longer considered clinically significant or judged medically stabilized by the Investigator or Medical Monitor. Clinically significant abnormal laboratory results should be reported as an AE or SAE if applicable.
- If such values do not return to normal/Baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor must be notified.
- All protocol-required laboratory assessments, as defined in Appendix B, must be conducted in accordance with the Laboratory Manual and the SOA (see Section 1.3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF and the laboratory reports must be filed with the source documents.

8.2.5 PREGNANCY TESTING

All WOCBP will have a serum pregnancy test (SPT) at screening and urine pregnancy test (UPT) at all designated post-screening timepoints as indicated in the SOA (Section 1.3). If UPT is positive, a serum pregnancy test will be performed to confirm. If any result is positive prior to investigational product administration, the subject will not receive study drug and will be discontinued. Follicle stimulating hormone (FSH) may be used to confirm menopausal status in female subjects as needed. Refer to Appendix C for further information.

8.3 PHARMACOKINETICS

Whole blood samples of approximately 5 mL will be collected for measurement of serum concentrations of etokimab at time points as specified in the SOA (see Section 1.3). A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Samples will be used to evaluate the PK of etokimab. Each serum sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of etokimab serum concentration may also be used to correlate exposure to safety or efficacy aspects related to concerns arising during or after the study.

Measurement of concentrations of etokimab will be performed using a validated assay method. Only samples which are within the window of sample stability will be analyzed. Placebo samples will not be analyzed. The time points for PK sample collection are given in Appendix L.

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

Genetic analyses will not be performed on these samples unless consent for this was included in the ICF. Subject confidentiality will be maintained. Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study center study files but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF. If a subject refuses blood collection for PK analysis, this will not be considered a protocol deviation as the PK analysis is an exploratory objective.

8.4 BIOMARKERS

Biomarkers are not evaluated in this study.

8.5 IMMUNOGENICITY

Antibodies to etokimab will be evaluated in serum samples collected from all subjects according to the SOA (See Section 1.3). Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for immunogenicity testing and a back-up).

Serum samples will be screened for antibodies binding to etokimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment.

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

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

8.6 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.6.1 DEFINITION OF ADVERSE EVENTS (AE)

The definitions of an AE or SAE can be found in Appendix M.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on the AEs, including that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 7.2).

8.6.2 TIME PERIOD AND FREQUENCY FOR COLLECTING AE AND SAE INFORMATION

All AEs will be collected from the signing of the ICF until the EOS visit at the time points specified in the SOA (see Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix M. The Investigator will submit any updated SAE data to IQVIA Lifecycle Safety email address (*QLS_Anaptys@quintiles.com*) within 24 hours of it being available. Electronic data capture is primary method of reporting SAEs, and the SAE form should only be sent to email address if the electronic data capture is offline or unavailable for some reason.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the IQVIA Lifecycle Safety.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix M.

8.6.3 METHOD OF DETECTING AES AND SAES

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.6.4 FOLLOW-UP OF AES AND SAES

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix M.

8.6.5 REGULATORY REPORTING REQUIREMENTS FOR SAES

Regulatory reporting requirements for SAE are as below:

- Prompt notification by the Investigator to the IQVIA Lifecycle Safety team of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The IQVIA Lifecycle Safety team has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.
- The IQVIA Lifecycle Safety team will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional review board/Independent Ethics Committee, and Investigators. Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and IQVIA Lifecycle Safety policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the IQVIA Lifecycle Safety team will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Upon checking serious on the AE eCRF, a notification will be sent to the Medical Monitor and/or designee. Relevant eCRFs, including the subject's Medical History, Concomitant Medications, and other AEs must also be completed to provide supporting documentation for the SAE. If there are additional documents that support the SAE (eg, clinic or hospital records or procedure reports), they should be uploaded to the AE eCRF.
After review of the initial SAE report, the Medical Monitor may request additional documentation. The Sponsor is responsible for notifying the relevant Regulatory Authorities of certain events. It is the Investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, study drug-related events that occur during any other clinical trial of etokimab. The Investigator is responsible for notifying its IRB/IEC of these additional SAEs.

8.6.6 PREGNANCY

- Details will be collected on all pregnancies occurring from after the start of study treatment and until at least 16 weeks after the last dose.
- Details of all pregnancies in female partners of male subjects will be collected while the male subject is in this study and until at least 16 weeks after the last dose.
- If a pregnancy is reported, the Investigator should inform IQVIA Lifecycle Safety within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix C.
- If a pregnancy occurs, it will be followed-up to determine the outcome, but no longer than 4 weeks after the estimated delivery date.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.6.7 OVERDOSE OF STUDY DRUG

For subject overdose (ie, dosing errors resulting in the administration of an SC dose that is more than 2 times the assigned dose), the Investigator or designee should:

1. Monitor the subject clinically:
   - Supportive measures are to be undertaken as clinically indicated.
   - Electrocardiography and clinical laboratory evaluations (ie, blood glucose, hepatic enzymes, creatinine, blood urea nitrogen, creatine kinase, and complete blood count) are to be performed and, **if abnormal**, followed until all values return to baseline levels and AEs subside.
   - Upon evaluation of the subject, the Investigator or designee should contact the Medical Monitor to discuss continued participation.

2. Record a protocol deviation.

3. If the event meets the definition of an AE or SAE, as per Appendix M:
   - Document and report an AE/SAE associated with the overdose.
   - Contact the Medical Monitor immediately (within 24 hours of learning of the event [Section 8.6.5]).

8.7 UNANTICIPATED PROBLEMS

8.7.1 DEFINITION OF UNANTICIPATED PROBLEMS

According to ICH and Industry requirements this protocol considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

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

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

8.7.2 UNANTICIPATED PROBLEM REPORTING

The Investigator will report UPs to the reviewing IRB/IEC and to IQVIA Lifecycle Safety team. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB/IEC project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB/IEC and to IQVIA Lifecycle Safety team within 24 hours of the Investigator becoming aware of the event.
- Any other UP will be reported to the IRB/IEC and to IQVIA Lifecycle Safety team within 7 days of the Investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the FDA within 14 days of the IRB's/IEC's receipt of the report of the problem from the Investigator.

8.7.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

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

9 STATISTICAL CONSIDERATIONS

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the total population for each treatment arm.

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will provide details about describe the subject analysis data sets to be included in the analyses of the primary, secondary and exploratory endpoints, and missing data strategies/procedures for accounting for missing, unused, and spurious data, testing strategies, among other details.

PK analyses will be detailed in the Pharmacokinetic Analysis Plan. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Ad hoc exploratory analysis may be performed in addition to those specified, but no claims or conclusions will be drawn other than hypotheses to be tested in future clinical trials.

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

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.

9.1 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, a total sample of approximately 300 subjects (60 subjects per treatment arm) 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 arm respectively) with a covariate R-squared of 0.300.

9.2 STATISTICAL HYPOTHESIS

Statistical hypotheses and testing utilized will be defined in the SAP, including the null and alternative hypotheses. Primary, secondary, and exploratory endpoint analyses will all be included in the SAP.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the analysis sets are defined in Table 6.

Table 6. 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 safety analysis set 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 full analysis set 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).
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 or events with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

9.4 BASELINE DEFINITION

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

9.5 EFFICACY ANALYSES

Descriptive statistics for absolute and change from Baseline by visit will be provided for all continuous primary, secondary, and exploratory efficacy endpoints.

Categorical end points will be summarized using frequency and percentage. By-subject listings will also be provided. Primary, secondary, and exploratory endpoints will be analyzed as described below.

9.5.1 PRIMARY EFFICACY ENDPOINT

Percent change in EASI score from Baseline to Week 16 will be analyzed using an ANCOVA model adjusting for baseline EASI score in the FAS.

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.

9.5.2 SECONDARY AND EXPLORATORY ENDPOINTS

All secondary binary endpoints will be analyzed using a logistic regression adjusting for baseline EASI score.

For all continuous endpoints, an ANCOVA model (similar to the analysis for the primary endpoint) will be used.

9.5.3 MULTIPLICITY

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% level is not achieved.

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

Testing of secondary Endpoints:

A gatekeeping procedure around the primary endpoint will be used: if at least 1 of the comparisons between the active treatments vs placebo crosses the 0.05 alpha boundary (statistical significance) then all secondary endpoints will be tested in a hierarchical approach. The order / sequence for testing all secondary endpoints will be described in the SAP.

9.5.4 HANDLING OF DROPOUTS AND MISSING DATA

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

Nonetheless, as subjects may elect to be withdrawn from study treatments or evaluations without prejudice, it is inevitable that there will be missing data.

For subjects who receive rescue therapy and are considered nonresponders according to Section 6.5.2, the data collected after rescue treatment is initiated will be treated as missing.

Missing efficacy data will be imputed using Multiple Imputation (MI) Procedure which will be detailed in the SAP. Additional missing data strategies will be used as deemed appropriate.

Safety data will not be imputed.

9.6 SAFETY ANALYSES

For safety and tolerability, AEs, SAEs, vital signs, ECGs, ADA, neutralizing antibodies, and clinical laboratory assessments at specific time points will be evaluated. All safety data will be summarized descriptively. 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, hematology, 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. The Baseline will be the last assessment obtained before the first dose.

Additional safety analysis will be also provided as deemed appropriate. Details will be provided in the SAP.

9.6.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A treatment-emergent adverse event (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.

Only TEAEs will be summarized.

Adverse events will be coded using MedDRA. Number of events and percentage will be tabulated by preferred term (PT) and system organ class (SOC). An event that occurred 1 or more times during a treatment period will contribute 1 observation to the numerator. The denominator will consist of all subjects in the SAF. If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences. The AEs, SAEs, TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to withdrawal of subject, and TEAEs leading to death will be listed and summarized by SOC and PT. Summaries will also be presented by relatedness to the study drug and severity.

Injection site reactions will be reported separately by treatment.

9.6.2 DEATHS

The following death summaries will be generated:

- Number (%) of subjects who died by study period (TEAE, on-study) and reasons for death summarized for the SAF by treatment received.

- Death in nonrandomized subjects or randomized and not treated subjects.

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

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

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

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

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

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

9.6.4 SUBJECT DISPOSITION

A summary of subject disposition will be provided using the SAF. It will include the number of subjects screened, randomized, treated, completed as well as the number of dropouts, with reasons for discontinuation, and major protocol deviations.

A listing will be presented to describe date of screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations will be identified and approved by the Investigator and Sponsor during the dry run to categorize deviations as major or minor.

9.6.5 SUBJECT CHARACTERISTICS AND MEDICAL HISTORY

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

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

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

9.6.6 CONCOMITANT MEDICATIONS

All medications will be coded using the World Health Organization Drug Dictionary. Each medication will be classified as prior medication if it is stopped prior to the first dose of study drug, or as concomitant

medication if it is ongoing at the time of the first dose or is started after the first dose of study drug. Prior, concomitant, and rescue medications will be summarized by ATC level 2 categories, and preferred name.

9.7 INTERIM ANALYSES

An Interim Analysis (IA) will be performed when all active subjects complete their Week 16 visit for final assessment of all primary and secondary efficacy endpoints (for Week 16) and all safety data available (up to Week 24). Final database lock will include exploratory efficacy and safety analysis for all subjects for Weeks 20 and 24.

9.8 SUBGROUP ANALYSES

Subgroup analyses will be detailed in the SAP.

9.9 IMMUNOGENICITY ANALYSES

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

9.10 OTHER ANALYSES

Pharmacokinetic analyses will be described in a PK modeling and simulation analysis plan, separate from the SAP, and finalized before database lock. The population PK analysis will be presented separately from the main clinical study report in a PK modeling and simulation report.

Serum etokimab concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. Pharmacokinetic concentration data collected from the study may be included in a population PK based (meta-) analysis, using non-linear mixed effects modeling. The data from this study may be combined with data collected from other studies for population PK model development.

The primary PK parameters of CL/F and Vd/F will be estimated by population PK modeling from etokimab serum concentrations after SC administrations. Secondary PK parameters (AUC_{τ}, C_{max}, and t_{max} for the first dose, and AUC_{τ}, C_{max}, t_{max}, and $t_{1/2}$ for the last dose) will also be calculated for etokimab after SC administrations, where possible, using a Bayesian post-hoc estimation approach based upon the aforementioned population PK model. The PK parameters will be listed and summarized using appropriate descriptive statistics. A covariate screen of subject specific factors (eg, demographic and clinical characteristics) will be included in the analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed Consent Process is as follows:

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons may include safety, among others. Should the Sponsor decide to terminate the study, the Investigator(s) will be notified in writing.

Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, with International Conference on Harmonisation-Good Clinical Practice (ICH-GPC) guidelines, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, FDA guidelines and regulations, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data

entry and study management systems used by clinical study sites and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

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

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

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

With the subject's approval and as approved by local IRBs/IECs, de-identified biological samples will be stored at a certified, licensed central laboratory. These samples may be used to research the causes of AD, its complications and other conditions for which individuals with AD are at increased risk, and to improve treatment. The central lab will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each subject, maintaining the blinding of the identity of the subject.

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

Samples will be stored at least until completion of study, which refers to signed CSR, with preference to store samples up to 5 years following EOS. If a subject withdraws from study prior to analysis, samples collected from the subject may be destroyed following written notification to Sponsor and Sponsor confirming approval to destroy in writing as well. Sponsor will also provide in writing any instructions if samples are to be destroyed sooner than the 5-year limit.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Table 7 lists the key personnel for this study. Additional study contact information will be provided in the Study Operations Manual.

Table 7. Key Study Personnel for Protocol ANB020-005

Medical Monitor Sponsor [redacted]
AnaptysBio, Inc.
10421 Pacific Center Court, Suite 200, San Diego, CA 92121 USA
(858) 362-6295 (general line)
ANB020-005@anaptysbio.com

10.1.6 DATA AND SAFETY MONITORING BOARD

An independent DSMB will be constituted by the contract research organization (CRO) to oversee the safety aspects of this study. The DSMB will also include a specialist from different disciplines/specialties as per the written charter. The DSMB will examine the safety data emerging from the study and provide its recommendations to the Sponsor who will then pass these on to PIs and/or the IEC/IRB according to requirements and regulations. DSMB members will not be investigators in the study nor will they have any conflict of interest with the Sponsor.

The planned approach for data provided to the DMSB is as follows:

- DSMB DRM #1 approximately 25% Enrollment
- 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.

The identification/affiliation of DSMB members, roles and responsibilities of the DSMB, the operational procedures, data review meeting (DRM) schedules, data cutoff period/dates for review and method of communication with the CRO and/or Sponsor will be described in a separate DSMB charter.

10.1.7 CLINICAL MONITORING

Sponsor has engaged the services of a contract research organization, IQVIA, to perform all monitoring functions within this clinical study. IQVIA Monitors will work in accordance with IQVIA standard operating procedures (SOPs). The Monitor will establish and maintain regular contact between the Investigator and Sponsor.

Monitoring will be carried out as determined by risk assessment process conducted on the study.

The Monitor will evaluate the competence of the study center, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, the Monitor will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. The Monitor is also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. The Monitor will also assess and control adherence to the protocol and ICH/GCP guidelines at the study center. The Monitor will arrange for the supply of study treatment, ensure proper study treatment dispensing/accountability, and appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification). For the following and all other items, this check will be 100%:

- Subject identification number.
- Subject consent obtained.
- Subject eligibility criteria (inclusion and exclusion criteria).
- Efficacy variables.
- Safety variables.
- Medical record of AE.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

According to the Guidelines of GCP (CPMP/ICH/135/95), IQVIA is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs). Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Central laboratories for clinical laboratory parameters.
- Center Initiation visit and/or participation in an Investigator Meeting.
- Early center visits post-enrollment.
- Routine center monitoring.
- Ongoing center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, Sponsor and/or IQVIA Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study center, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of IQVIA.

Electronic data capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The Clinical Site Monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The Monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the center staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible Monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include but are not limited to laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study Monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study treatment, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be

facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

10.1.9.2 STUDY RECORDS RETENTION

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study treatment (etokimab). These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. No study records should be destroyed without prior authorization from the Sponsor.

10.1.10 PROTOCOL DEVIATIONS

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

It is the responsibility of the study center Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

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

- Failure to meet inclusion/exclusion criteria as defined by protocol
- 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
- Partial dosing of study treatment
- Use of prohibited concomitant medications unless defined as rescue medication per protocol
- Study procedures done outside protocol-specified window period that are judged to affect study efficacy data
- Assessments for primary endpoint not done.

Protocol deviations will be reviewed prior to unblinding and individual subjects having protocol deviations will be evaluated for inclusion in the PPS. Any additional deviations not listed above will be documented at this time. Further details about the handling of protocol deviations will be included in the Protocol Deviation Plan, Clinical Operations Plan, Medical Monitoring Plan, Safety Management Plan, and SAP.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Medical Monitor and the Sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the Medical Monitor.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests in accordance to local requirements and laws during the course of the study and for 1 year after completion of the study.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.

- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

10.2.2 AMENDMENT POLICY

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

10.3 ABBREVIATIONS

Abbreviation	Definition
ACQ-6	Asthma Control Questionnaire-6
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{τ}	Area under the concentration-time curve for a dosing interval
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CFR	Code of Federal Regulations
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
eCRF	Electronic case report forms
EOS	End of Study
ePRO	Electronic patient reported outcome
ETV	Early termination visit
FAS	Full analysis set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigators Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN- γ	Interferon gamma
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IGRA	Interferon-gamma release assay
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
IXRS	Interactive Web Response System
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimal clinically important difference

Abbreviation	Definition
NCT	National Clinical Trial
NRS	Numerical rating scale
PI	Principal investigator
PK	Pharmacokinetics
POEM	Patient Oriented Eczema Measure
PPS	Per protocol Analysis Set
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SOA	Schedule of Activities
SOC	System organ class
SOP	Standard Operating Procedure
ST2	IL-33 receptor
$t_{1/2}$	Apparent terminal half-life
TB	Tuberculosis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	T helper type 2
t_{max}	Time of maximum concentration
ULN	Upper limit of normal
UP	Unanticipated problem
US	United States
Vd/F	Apparent volume of distribution
vIGA-AD	Validated Investigator Global Assessment Scale for Atopic Dermatitis
WOCBP	Woman of childbearing potential

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APPENDICES

APPENDIX A: SUMMARY OF CHANGES FOR (COUNTRY-SPECIFIC) AMENDMENT 1

The summary of changes for global amendment 2 are shown in Table 8.

Table 8. Summary of Changes for ANB020-005 Protocol Amendment 2

Affected Section(s)	Summary of Revisions Made	Rationale
Entire protocol	• Sections and Appendices reordered, added, and/or deleted	• Consistency with new Common Protocol Template
Sponsor Signature Page	• Updated statement of Sponsor's compliance and approval of protocol	• Consistent with ICH expectations of Sponsor obligations and AnaptysBio use of Common Protocol Template
Synopsis, Sections 1.3 (footnote 'o'), 8.7	• Revised description of administration of ACQ-6 to subjects whose primary language is English and availability of validated translations in participating countries	• Accuracy and completeness
Synopsis, Section 4.1	• Added statement that DSMB would also advise the Sponsor of potential safety signals	• Accuracy and completeness
Synopsis	• Revised the number of study centers and added the geographic regions of study centers	• Accuracy and completeness
Figure 1	• Revised figure caption and simplified study population bullet in figure	• Accuracy and completeness
Section 1.3 (SOA table)	• Deleted 'Optional items informed consent' at screening from table • Revised footnote 'g' to specify that a negative pregnancy test result must be obtained at Visits 1 and 2 before subject may be randomized into study • Revised table and footnote 'h' to include TB testing, on a country-by-country basis • Clarified and revised timepoints for hematology and chemistry blood samples (footnote 'I'), urinalysis (footnote 'j'), and PK blood samples (footnote 'k')	• Provide clarification the optional ICF is not a separate item from the informed consent • Assuring patient safety requirement and compliance with health authority requests • Accuracy and completeness
Section 2.1	• Revised the description of the mechanism of action of etokimab with respect to IL-33 inhibition and added 2 new references.	• Consistency with Etokimab IB version 7

Affected Section(s)	Summary of Revisions Made	Rationale
Section 2.2.2	• Added statement that etokimab and ANB020 are used interchangeably throughout the study protocol • Updated atopic diseases that etokimab is being developed to treat	• Accuracy and completeness • Consistency with Etokimab IB version 7
Section 2.2.2.2	• Added summary statement	• Completeness
Section 2.2.2.2.1	• Updated summary of Study ANB020-001 results	• Consistency with version 7 of the Etokimab IB
Section 2.2.2.2.2	• Added summary of Study ANB020-BA-01 results	• Consistency with version 7 of the Etokimab IB
Section 2.2.2.2.3	• Added summary of Study ANB020-002 results	• Consistency with version 7 of the Etokimab IB
Section 2.3.1	• Updated known potential risks of etokimab	• Consistency with version 7 of the Etokimab IB
Section 3	• Provided justification for endpoints	• Accuracy and clarification
Section 4.3	• Justification of dose	• Health authority request for clarity and completeness
Section 4.4	• Revised end of study definition to include last visit on Day 169 or the last scheduled procedure	• Aligning with industry standard definition
Section 5.1	• Inclusion Criterion #2: Revised maximum BMI to ≤35 kg/m^2 for all subjects • Inclusion Criterion #4: Expanded EASI score at screening and Baseline from ≥12 to ≥16 at screening and Baseline • Inclusion Criterion #7.b.ii: Added restriction to WOCBP to refrain from donating oocytes during treatment period and at least 3 months after last dose of study drug	• Focusing on patient safety and aligning criteria in patients being enrolled • Input provided by participating clinical investigators with strong patient management experience • Complying with the Health Authorities request
Section 5.2	• Exclusion Criterion #14: Added note to better define how TB will be diagnosed and deleted text about TB retesting. • Exclusion Criterion #16: Revised permissible hemoglobin, neutrophils, and platelets levels at screening • Exclusion Criterion #17: Replaced history of drug abuse criterion with a new drug/substance abuse criterion	• Complying with the Health Authority requests. • Providing clarification on drug, alcohol or other substance abuse criteria.
Section 5.4	• Updated number of re-screens allowed	• Correction
Section 6.2.2	• Updated description of etokimab formulation	• Consistency with Etokimab IB version 7.0
Section 6.2.4	• Added IP preparation details	• Clarification regarding site expectation to comply with IP preparation and preserving blind.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 6.2.5	• Added additional dosing instructions	• Health authority requests to assure no overlap between injection sites.
Section 6.5.2	• Added details regarding anti-inflammatory topical rescue therapy	• Provide clarification
Section 7.1	• Added details to better define discontinuation of study intervention	• Provide clarification
Section 7.2	• Revised ALT or AST criteria for discontinuation/withdrawal from study	• Assuring patient safety requirement and compliance with health authority requests
Section 7.3	• Revised description of rescheduled and missed visits	• Provide clarification
Section 8.2	• Added statement that unscheduled safety assessments may be performed at any time during the study.	• Provide clarification
Section 8.3	• Updated PK and ADA processing	• Clarification
Sections 8.7, 8.7.1, 8.7.2, 8.7.3	• Added new section for Unanticipated Problems	• Consistent with new Common Protocol Template language
Section 9.1	• Updated statistical hypothesis	• Clarification
Section 9.3.2	• Modified the endpoint to NRS for pruritus score reduction from Baseline of 4.	• Per scientific advice per the health authority
Section 9.3.2.4	• Added new section for the handling of dropouts and missing data	• Clarification and aligning with industry practice
Section 9.3.6	• Added new section for subgroup analyses	• Common Protocol Template language
Section 9.3.9	• Revised PK parameters and identified the Bayesian post-hoc estimation approach as the PK simulation model to be used	• Accuracy and completeness
Section 10.1.2	• Added examples to possible study discontinuation and closure	• Assuring Sponsor obligation to oversee and manage site performance.
Section 10.1.4	• Added guidelines around sample storage and notification of destruction	• Provide clarification and assuring site understanding of process
Section 10.1.10	• Added section for protocol deviations	• Consistent with new Common Protocol Template
Appendix A	• Added new appendix for Amendment 1 Summary of Changes	• Provide clarification

The Summary of Changes for each of the 3 country-specific protocol amendments for ANB020-005 Protocol Amendment 1 are shown in Table 9. (Czech Republic), Table 10 (Germany), and Table 11 (the UK).

Table 9. Protocol Amendment 1 for Czech Republic (dated 01 August 2018)

Affected Section	Original Text	New Text	Rationale
1.3 Schedule of Activities and footnote (p. 15)		In addition, tuberculosis testing by interferon-gamma (IFN-γ) release assay (IGRA) will be performed on a country-by-country basis if required by regulatory authorities (eg, Czech Republic) or ethics boards.	Added IGRA test to exclude latent forms of TBC if negative test result is required for eligibility.
4.3 Justification for Dose (p. 26)	Emergent data from the Phase I study (ANB020-001) and Phase IIa study (ANB020-002) are the basis for the section of dose of ANB020 for the current study. The 300 mg IV dose was found to be safe and well tolerated in healthy subjects and in subjects with AD. An interim analysis of the Phase IIa study indicated that a clinical response was observed 2 weeks post ANB020 administration (300 mg IV). One month post ANB020 administration, the average EASI score reduction was 61% and the average pruritus reduction was 32 % relative to Baseline. Sustained clinical response was observed after 2 months post-ANB020 administration. The Phase I study in healthy subjects is completed. The dose range of ANB020 (excluding the expected sub-therapeutic 20 mg, and placebo arms) selected for this study has provided complete inhibition of IL-33 induced cytokine release, and has been used safely in study ANB020-001.	Data from the Phase I study (ANB020-001) and Phase IIa study (ANB020-002) are the basis for the selection of dose of ANB020 for the current study. The dose range of ANB020 selected for this study has been used safely in study ANB020 001. ANB020 pharmacodynamic activity, measured as inhibition of ex-vivo IL-33 stimulated INF-γ production, can be inferred from the correlation with PK data. All of the selected dose levels of ANB020 are predicted to induce full IL-33 inhibition within 2 days for at least 9-10 days after dosing. The administration of the loading doses of ANB020 will allow systemic concentrations to reach serum concentrations sustaining more than 95% IL-33 inhibition faster, and potentially reduce the time to onset of clinical effect. Data from the Phase IIa study show a clinical response 1 week post ANB020 administration (300 mg IV), and the dose was found to be safe and well tolerated. One month post ANB020 administration, the average EASI score reduction was 61% and the average pruritus reduction was 32 % relative to Baseline. Sustained clinical response was observed after 2 months post-ANB020 administration.	Provided additional clarification on rationale for dose.
Exclusion criteria (p. 29)	14. Immunodeficiency disorders (eg, IgA deficiency) or known or	14. Immunodeficiency disorders (eg, IgA deficiency) or known or	Provided additional clarification on eligibility for

Affected Section	Original Text	New Text	Rationale
	suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocytosis, aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per Investigator's judgement.	suspected history of immunosuppression, including history of invasive opportunistic infections (eg, active or latent tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocytosis, aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per Investigator's judgement. NOTE: Suspected active or latent tuberculosis will be based on medical history, physical examination, and standard of care diagnostic methods. Subjects with a positive interferon-gamma (IFN-γ) release assay (IGRA) at screening are not eligible for this study.	subjects with suspected tuberculosis.
Exclusion criteria (p. 30)	16. Laboratory findings at screening: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) and total bilirubin >2 times ULN (except in case of documented Gilbert's syndrome) at screening. • Confirmed AST and/or ALT >5 × ULN. • Hemoglobin is <9 g/dL. • Neutrophils <1.0 × 103/µL. • Platelets <100 × 103/µL.	16. Laboratory findings at screening: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN). • Hemoglobin is <11 g/dL. • Neutrophils <1.5 × 103/µL. • Platelets <100 × 103/µL.	Changed requirements for laboratory findings at screening to exclude subjects with more severe abnormalities in their liver enzymes or hematology levels.
Abbreviations (p. 60)		IGRA Interferon-gamma release assay	Added additional abbreviation.
Table 10 Protocol-required Safety Laboratory Assessments (p. 70)		Interferon-gamma release assay (if required on a country-by-country basis)	Added IGRA test to exclude latent forms of TBC if negative test result is required for eligibility.

Table 10. Protocol Amendment 1 for Germany (dated 31 July 2018)

Affected Section	Original Text	New Text	Rationale
4.3 Justification for Dose (p. 26)	Emergent data from the Phase I study (ANB020-001) and Phase IIa study (ANB020-002) are the basis for the section of dose of ANB020 for the current study. The 300 mg IV dose	Data from the Phase I study (ANB020-001) and Phase IIa study (ANB020-002) are the basis for the selection of dose of ANB020 for the current study. The dose range of	Provided additional clarification on rationale for dose.

Affected Section	Original Text	New Text	Rationale
	was found to be safe and well tolerated in healthy subjects and in subjects with AD. An interim analysis of the Phase IIa study indicated that a clinical response was observed 2 weeks post ANB020 administration (300 mg IV). One month post ANB020 administration, the average EASI score reduction was 61% and the average pruritus reduction was 32 % relative to Baseline. Sustained clinical response was observed after 2 months post-ANB020 administration. The Phase I study in healthy subjects is completed. The dose range of ANB020 (excluding the expected sub-therapeutic 20 mg, and placebo arms) selected for this study has provided complete inhibition of IL-33 induced cytokine release, and has been used safely in study ANB020-001.	ANB020 selected for this study has been used safely in study ANB020-001. ANB020 pharmacodynamic activity, measured as inhibition of ex-vivo IL-33 stimulated INF-γ production, can be inferred from the correlation with PK data. All of the selected dose levels of ANB020 are predicted to induce full IL-33 inhibition within 2 days for at least 9-10 days after dosing. The administration of the loading doses of ANB020 will allow systemic concentrations to reach serum concentrations sustaining more than 95% IL-33 inhibition faster, and potentially reduce the time to onset of clinical effect. Data from the Phase IIa study show a clinical response 1 week post ANB020 administration (300 mg IV), and the dose was found to be safe and well tolerated. One month post ANB020 administration, the average EASI score reduction was 61% and the average pruritus reduction was 32 % relative to Baseline. Sustained clinical response was observed after 2 months post-ANB020 administration.	
6.5.6 Rescue Medicine (pg. 37)	Subjects who are rescued should receive low potency TCS over moderate or high potency TCS.	Anti-inflammatory topical rescue therapy should be administered to lesional skin only. The choice of the corticosteroid should be based upon standard of care considerations (eg, body area involved, severity of skin inflammation). A list of representative topical corticosteroids is provided in Appendix 15. We suggest a low potency corticosteroids (Class 6/7) cream or ointment. If needed for more severe inflammation, we suggest moderate potency corticosteroids (Class 4/5). Topical calcineurin inhibitors (eg, tacrolimus	Provided additional clarification on the rescue medications.

Affected Section	Original Text	New Text	Rationale
		0.1%) may be an alternative to topical corticosteroids, in particular for the treatment of the face, neck, and skin folds.	
Appendix 2 Regulatory, Ethical, and Study Oversite Considerations (pg. 68)		Reasons may include safety, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.	Provided possible reasons for study termination by the Sponsor
Appendix 15 WHO Classification of Topical Corticosteroids (pg. 95)		WHO Classification of Topical Corticosteroids Topical corticosteroids have been ranked in terms of potency into four groups consisting of seven classes. Class I topical corticosteroids are the most potent and Class VII are the least potent. Representative preparations by group are listed in the table below. These groups may vary depending on the formulation and concentration and should be considered approximate.	Reference provided as guidance to the rescue medication

Table 11. Protocol Amendment 1 for the UK (dated 21 June 2018)

Affected Section	Original Text	New Text	Rationale
Inclusion Criteria #7 ii (p. 27)	A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment period and for at least 3 months after receiving the last dose of study treatment.	A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment period and for at least 3 months after receiving the last dose of study treatment and refrain from donating oocytes (eggs) during this period.	It is not known whether ANB020 affects reproductive capacity. Therefore, women of childbearing potential should take necessary precautions to avoid pregnancy while receiving ANB020. This includes the donation of their eggs to achieve pregnancy in assisted reproductive care.
Exclusion Criteria #16 (p. 29)	Laboratory findings at Screening: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) and total bilirubin >2 times ULN (except in case of documented Gilbert's syndrome) at screening. • Confirmed AST and/or ALT >5 × ULN. • Hemoglobin is <9 g/dL.	Laboratory findings at screening: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) <u>and</u> total bilirubin >1.5 times ULN (total bilirubin >3 times ULN in case of documented Gilbert's syndrome) at screening.	The safety profile of ANB020 is evolving and the minimum allowed hematology and bilirubin levels were at the limit of risk. Added a missing upper limit for total bilirubin in case of Gilbert's syndrome (GS). GS is a benign condition characterized by higher than normal levels of unconjugated bilirubin, usually in the range of 1-3 × ULN (eg, after fasting).

Affected Section	Original Text	New Text	Rationale
	• Neutrophils <1.0 × 10^3/µL. • Platelets <100 × 10^3/µL.	• Confirmed AST and/or ALT >5 × ULN. • Hemoglobin is <10 g/dL. • Neutrophils <1.5 × 10^3/µL. • Platelets <150 × 10^3/µL.	
7.2 Subject Discontinuation/ Withdrawal from the Study (p. 37)	• Laboratory abnormalities: o ALT or AST >5 times ULN for more than 2 weeks. o ALT or AST >3 times ULN and bilirubin >2 times ULN (unless related to Gilbert's syndrome) at screening visit.	• Laboratory abnormalities: o ALT or AST >5 times ULN for more than 2 weeks. o ALT or AST >3 times ULN and bilirubin >2 times ULN (total bilirubin >4 times ULN in case of documented Gilbert's syndrome).	Added upper limit for total bilirubin in case of Gilbert's syndrome. Levels of bilirubin can fluctuate in people with Gilbert's syndrome. They may be highest during certain conditions (eg, infection, fasting, or menstrual periods), but rarely exceed 4 × ULN in these patients.
Appendix 6 Contraceptive Guidance – Female Subjects (p. 77)	Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below.	Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below and refrain from donating oocytes (eggs) for 3 months after receiving the last dose of study treatment	Same as above (p. 27).

APPENDIX B: CLINICAL LABORATORY TESTS

Clinical laboratory tests will be carried out at time points specified in the SOA (see Section 1.3).

- The tests detailed in Table 12 will be performed by the central laboratory.
- Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to take an immediate decision for any safety concerns. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Urine pregnancy dipstick will be performed at the study center prior to study treatment administration.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 12. Protocol-required Safety Laboratory Assessments

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

Laboratory Assessments	**Parameters**	
Urine pregnancy	Urine pregnancy dipstick (prior to study treatment administration)	
Urinalysis (dipstick test)	Bilirubin	pH
	Blood	Protein
	Glucose	Specific gravity
	Ketones	Urobilinogen
	Leukocyte esterase	
	Nitrites	
Immunoglobulin	Immunoglobulin E	
Drugs of Abuse (Urine drug screen)	Methamphetamine	Benzodiazepines
	Cocaine	Barbiturates
	Marijuana	Phencyclidine
	MDMA	Amphetamine
	Methadone	Oxycodone
	Opiate	TCA
	Ethanol	
Viral serology	Hepatitis B surface antigen	
	Hepatitis B and C Antibody	
	HIV Antibodies (HIV 1 and 2)	
TB testing	Interferon-gamma release assay (if required on a country-by-country basis)	
The results of each local test must be entered into the eCRF.		
Abbreviations: ADA = anti-drug antibody; eCRF = electronic case report form, HIV = Human Immunodeficiency Virus, MDMA = Methylenedioxymethamphetamine, PK = Pharmacokinetics and TCA=Tricyclic anti-depressants. NOTES: Please see Schedule of Activities (see Section 1.3) for laboratory tests time points. PK and ADA samples will be collected as detailed in the Schedule of Activities (see Section 1.3). Samples should be obtained prior to administering study drug if an administration coincides with the visit and before any hematology, or chemistry, samples to be drawn at that visit. The date and exact time of sample collection must be recorded.		

Investigators must document their review of each laboratory safety report.

APPENDIX C: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

    Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female:

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

Contraception Guidance

Male Subjects

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

Female Subjects

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

Highly Effective Contraceptive Methods

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

Pregnancy Testing

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

Collection of Pregnancy Information

Male Subjects with Partners who Become Pregnant

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

Female Subjects who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.6.5. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

APPENDIX D: EXCLUDED MEDICATIONS/THERAPY

Excluded medications/therapy is listed below in Table 13. The use of an excluded medication/therapy is a protocol deviation and must be recorded in the eCRF. The following medications will not be permitted during the study:

Table 13. Excluded Medication/Therapy

Treatment	Wash-out period
Any topical medication containing corticosteroids (TCS), calcineurin inhibitor (TCI), or crisaborole.	14 days prior to Day 1.
Any systemic treatment for AD (including systemic corticosteroids, immunosuppressants, or immunomodulating drugs or phototherapy, or use of a tanning booth.	4 weeks prior to screening.
Live attenuated vaccine.	4 weeks prior to screening through Day 1.
Investigational systemic treatment or biologic systemic treatment.	5 half-lives prior to screening.
Investigational or licensed or other anti-Th2-type cytokine (eg, IL-31, IL-5, and TSLP) and anti-ST2.	16 weeks or 5 half-lives (whichever is longer).

Abbreviation: IL = Interleukin, ST2 = specific cell surface receptor, Th2 = T-helper cell, TSLP = Thymic stromal lymphopoietin.

Note: Topical emollients are allowed during the study, except within 8 to 12 hours prior to the assessment.

APPENDIX E: WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

Topical corticosteroids have been ranked in terms of potency into four groups consisting of seven classes. Class I topical corticosteroids are the most potent and Class VII are the least potent. Representative preparations by group are listed in the table below. These groups may vary depending on the formulation and concentration and should be considered approximate.

Potency	Class	Topical corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%

	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

The WHO Essential Medicines and Health Products Information Portal was designed and is maintained by *Human Info NGO*. Last updated: December 6, 2017

APPENDIX F: ECZEMA AREA AND SEVERITY INDEX SCORE FOR THE SEVERITY OF ATOPIC DERMATITIS (EASI)

How to Use EASI

The EASI scoring system uses a defined process to grade the severity of the signs of eczema and the extent affected:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a score of between 0 and 6 based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

To aid in your body region grading you can use the diagrams in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a photographic atlas of suggested categories is available in Appendix 2

Remember: *Include only inflamed areas in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted-if a sign is present it should be at least mild (1).

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region Score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	X	X 0.1	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.4	
The final EASI score is the sum of the 4 region scores:							____ (0-72)

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Source: Schram et al.[9]

APPENDIX G: VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS (VIGA-AD™)

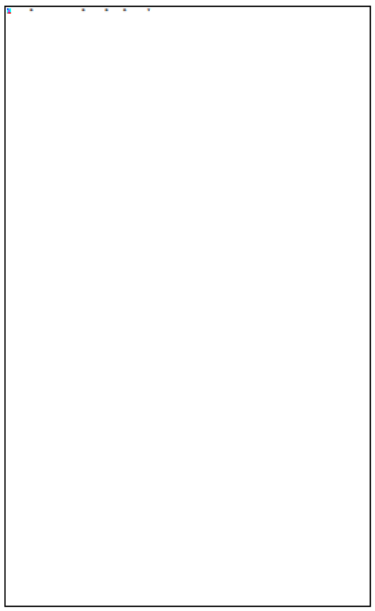
The vIGA-AD is a static 5-point scale to evaluate AD disease severity globally and is frequently assessed in clinical studies. Investigator vIGA-AD responses will be captured in eCOA tablet. The vIGA-AD result will be recorded at the time points indicated in the Section 1.3.

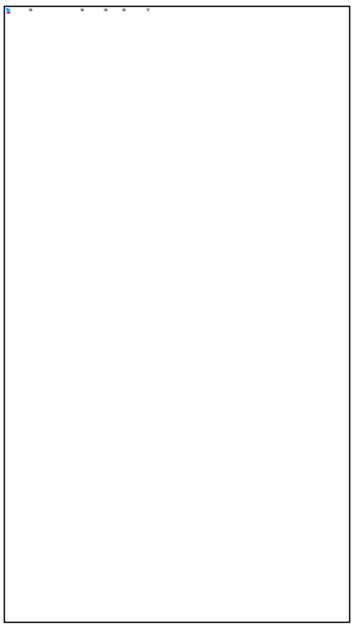
Score	Morphological Description
0- Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1-Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2-Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3-Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4-Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Source: Eli Lilly and Company.[10]

APPENDIX H: SCORING ATOPIC DERMATITIS FOR THE SEVERITY OF ATOPIC DERMATITIS (SCORAD)

Based on SCORAD European Task Force on Atopic Dermatitis





A. Extent of Area Involved

	Front				Back			
Head	☐ Not affected		☐ Affected		☐ Not affected		☐ Affected	
Upper limbs (left)	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area
Upper limbs (right)	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area
Lower limbs (left)	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area
Lower limbs (right)	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area
Trunk and Neck	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area	☐ 0	☐ 1/3	☐ 2/3	☐ Entire Area
Genitals	☐ Not affected		☐ Affected					
Hands	☐ None	☐ 1 hand	☐ Both hands		☐ None	☐ 1 hand	☐ Both hands	

B. Intensity

A representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as: 0= absent 1= mild 2=moderate 3= severe

Erythema (Redness)	☐ 0	☐ 1	☐ 2	☐ 3
Edema/papulation (Swelling)	☐ 0	☐ 1	☐ 2	☐ 3
Oozing / Crusting	☐ 0	☐ 1	☐ 2	☐ 3
Excoriations (Scratch marks)	☐ 0	☐ 1	☐ 2	☐ 3
Lichenification (Skin thickening)	☐ 0	☐ 1	☐ 2	☐ 3
Dryness*	☐ 0	☐ 1	☐ 2	☐ 3

*Dryness is evaluated on uninvolved areas

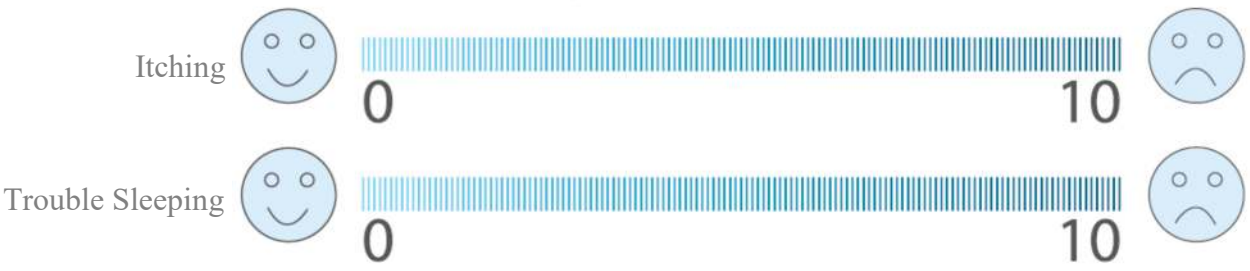
Intensity ☐

C: Subjective Symptoms: Pruritus + Sleep Loss:

Using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), patient to indicate the average value for the last 48 hours.

Patient facing:

Subjective Symptoms: Visual Analogue Scale Average for last 48 hours. Points from 0 to 10.



Subjective Symptoms Pruritus + Sleep Loss ☐

SCORAD **A/5 + 7B/2 +C**

☐

©1990 European Task Force on Atopic Dermatitis Published in "Dermatology in 1993; 186(1): 23-31 Consensus Report of the European Task Force on Atopic Dermatitis.[11]

How to record a SCORAD score:

Area:

To determine extent, the sites affected by eczema are shaded on a drawing of a body. The affected area (A) is calculated as a percentage of the whole body.

- Head 8%
- Upper limbs 9% each
- Lower limbs 18% each
- Hands 2% each
- Anterior trunk and neck 18%
- Back and neck 18%
- 1% for genitals.

The score for each area is added up. The total area is 'A', which has a possible maximum of 103%.

Intensity:

A representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Redness
- Swelling
- Oozing/crusting
- Scratch marks
- Skin thickening (lichenification)
- Dryness (this is assessed in an area where there is no inflammation)

The intensity scores are added together to give 'B' (maximum 18).

Subjective symptoms:

Subjective symptoms ie, itch and sleeplessness, are each scored by the subject or relative using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give 'C' (maximum 20).

Total score:

The SCORAD for that individual is A/5 + 7B/2 + C

APPENDIX I: DERMATOLOGY LIFE QUALITY INDEX SCORE FOR SEVERITY OF ATOPIC DERMATITIS (DLQI)

DLQI

Hospital No: Date:

Name: Score:

Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ ☐ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented	Yes	☐	

	you from **working** or **studying**?	No	☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	☐	
		A little	☐	
		Not at all	☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all ☐		Not relevant ☐

Please check you have answered EVERY question. Thank you.

Badia et al.[12]

APPENDIX J: PATIENT ORIENTED ECZEMA MEASURE (POEM)

POEM for self-completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): .....

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

• 0 to 2	= Clear or almost clear
• 3 to 7	= Mild eczema
• 8 to 16	= Moderate eczema
• 17 to 24	= Severe eczema
• 25 to 28	= Very severe eczema

Charman et al.[13]

APPENDIX K: SAMPLE ASTHMA CONTROL QUESTIONNAIRE-6 (ACQ-6)

ASTHMA CONTROL QUESTIONNAIRE-6 (ACQ-6)

Asthma Control Questionnaire **Subject ID:**

Date:

Please answer questions 1-6

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
	1	Hardly ever
	2	A few times
	3	Several times
	4	Many times
	5	A great many times
	6	Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0	No symptoms
	1	Very mild symptoms
	2	Mild symptoms
	3	Moderate symptoms
	4	Quite severe symptoms
	5	Severe symptoms
	6	Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
	1	Very slightly limited
	2	Slightly limited
	3	Moderately limited
	4	Very limited
	5	Extremely limited
	6	Totally limited
4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0	None
	1	A very little
	2	A little
	3	A moderate amount
	4	Quite a lot

Asthma Control Questionnaire		**Subject ID:** **Date:**
	5	A great deal
	6	A very great deal
5. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg Ventolin/Bricanyl) have you used each day? (*If you are not sure how to answer this question, please ask for help*)	0	None
	1	1-2 puffs/inhalations most days
	2	3-4 puffs/inhalations most days
	3	5-8 puffs/inhalations most days
	4	9-12 puffs/inhalations most days
	5	13-16 puffs/inhalations most days
	6	More than 16 puffs/inhalations most days
6. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time

APPENDIX L: PHARMACOKINETIC AND ANTI-DRUG ANTIBODY COLLECTION TIME POINTS

Study Day	Study Visit	PK Sample Time Point (Serum)	Sample Time Point for ADA
Day 1/Week 0 ANB020/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/ETV	11	Anytime during the study visit	Anytime during the study visit

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

APPENDIX M: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

AE Definition

- An AE is any untoward medical occurrence in a subject or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, and vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information (including event term, start and stop dates, severity, relationship to study treatment, outcome, if serious or non-serious) in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to IQVIA Lifecycle Safety in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by IQVIA Lifecycle Safety/Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to IQVIA Lifecycle Safety/Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, possibly related, related
    - "Unrelated": clinical event with an incompatible time relationship to study treatment administration, and that could be explained by an underlying condition or other drugs or chemicals or is incontrovertibly not related to the study treatment.
    - "Possibly related": clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals.
    - "Related": clinical event with plausible time relationship to study treatment administration and that cannot be explained by concurrent condition or other drugs or chemicals.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to IQVIA Lifecycle Safety. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IQVIA Lifecycle Safety.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IQVIA Lifecycle Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject died during participation in the study, the Investigator will provide IQVIA Lifecycle Safety with a copy of any postmortem findings.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the IQVIA Lifecycle Safety within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to IQVIA Lifecycle Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to IQVIA Lifecycle Safety will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section). • The study center will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given study center, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) and send the paper SAE form to IQVIA Lifecycle Safety team via facsimile transmission or email. • Contacts for SAE reporting can be found in SAE reporting form.

SAE Reporting to IQVIA Lifecycle Safety via Paper Case Report Form
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the IQVIA Lifecycle Safety team. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SAE reporting form.

APPENDIX N: HANIFIN AND RAJKA GUIDELINES FOR THE DIAGNOSIS OF ATOPIC DERMATITIS

1. Must have three or more basic features described below:
   (1) Pruritus
   (2) Typical morphology and distribution
      - Flexural lichenification in adults
      - Facial and extensor eruptions in infants and children
   (3) Chronic or chronically relapsing dermatitis
   (4) Personal or family history of atopy (asthma, allergic rhinitis, and atopic dermatitis)
2. Must have three or more following minor features:
   (1) Xerosis
   (2) Ichthyosis/palmar hyperlinearity, keratosis pilaris
   (3) Immediate (type I) skin test reaction
   (4) Elevated serum IgE
   (5) Early age of onset
   (6) Tendency toward cutaneous infections (especially Staph. aureus and Herpes simplex), impaired cell mediated immunity
   (7) Tendency toward non-specific hand or foot dermatitis
   (8) Nipple eczema
   (9) Cheilitis
   (10) Recurrent conjunctivitis
   (11) Dennie-Morgan infraorbital fold
   (12) Keratoconus
   (13) Anterior subcapsular cataracts
   (14) Orbital darkening
   (15) Facial pallor or facial erythema
   (16) Pityriasis alba
   (17) Anterior neck folds
   (18) Itch when sweating
   (19) Intolerance to wool ad lipid solvents
   (20) Perifollicular accentuation
   (21) Food intolerance
   (22) Course influenced by environmental and emotional factors
   (23) White dermographism or delayed blanch

Source: Hanifin et al.[8]