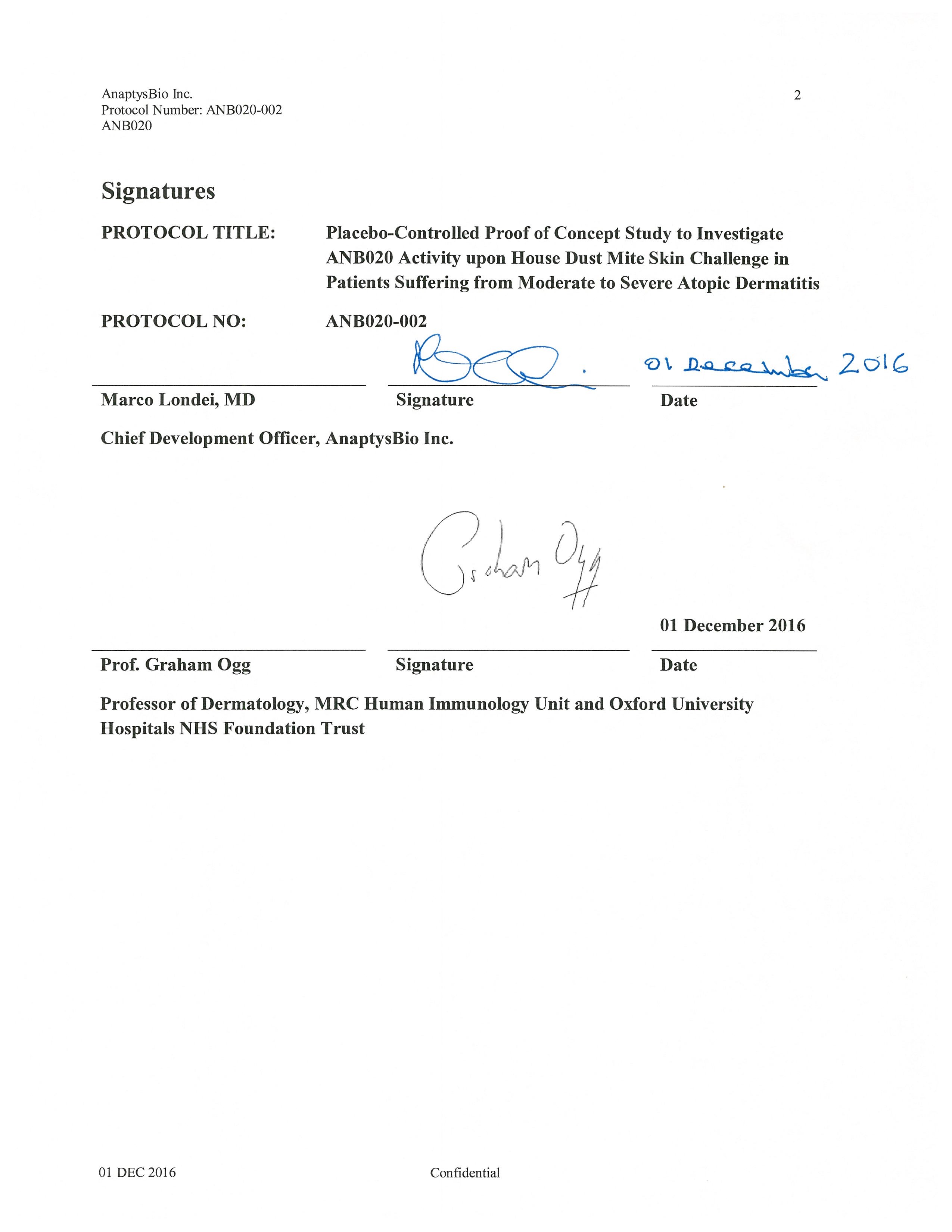
Protocol Number: ANB020-002

ANB020

**Clinical Study Protocol**

|  |  |
| --- | --- |
| **Protocol Title:** | **Placebo-Controlled Proof of Concept Study to Investigate**  **ANB020 Activity upon House Dust Mite Skin Challenge in**  **Patients Suffering from Moderate to Severe Atopic Dermatitis** |
| **Protocol Number:** | **ANB020-002** |
| **Version:** | **Amendment 2** |
| **Date of Protocol:** | **01 DEC 2016** |
| **Product:** | **ANB020** |
| **Pre-IND No.:** | **26765** |
| **EudraCT No.:** | **2016-002539-14** |
| **Study Phase** | **II** |
| **Sponsor:** | **AnaptysBio Inc.**  **10421 Pacific Center Court, Suite 200, San Diego, CA 92121, United States** |
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|  | Confidentiality Statement |

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**SYNOPSIS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of Sponsor/Company:** | | AnaptysBio Inc. | |
| **Name of Finished Product:** | | Humanized immunoglobulin subtype G1/kappa (IgG1/kappa) monoclonal antibody | |
| **Name of Active Ingredient:** | | ANB020 | |
| **Title of Study:** | Placebo-Controlled Proof of Concept Study to Investigate ANB020 Activity upon House Dust Mite Skin Challenge in Patients Suffering from Moderate to Severe Atopic Dermatitis | | |
| **Protocol No:** | ANB020-002 | | |
| **Investigators:** | Prof. Graham Ogg | | |
| **Study center:** | Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom | | |
| **Study duration:**  The expected duration of the study is approximately 23 weeks (162 days).  Screening 7-14 days and Treatment and Follow-up 148 days. | | | **Phase:**  II |
| **Objectives:**  Primary:   * To measure the decrease of cytokines within interstitial fluid, where saline and house dust mite (HDM) have been administered, in patients receiving ANB020 compared to placebo. * To assess the effect of ANB020 on differential white blood cell (WBC) counts. * To assess the safety and tolerability of single dose administration of ANB020 in patients with atopic dermatitis (AD).   Secondary:   * To assess the effect of ANB020 on serum cytokines. * To compare the changes in urticarial manifestation 0.5 hours after HDM challenge between patients receiving placebo and then ANB020. * To assess the PD activity of ANB020 on ex vivo induced interferon-gamma (IFN-γ) levels. * To test for any immunogenicity to ANB020. * To describe the limited pharmacokinetics (PK) of ANB020 following a single, intravenous (IV) dose.   Exploratory:   * To assess the effect of ANB020 on leukocytes within interstitial fluid. * To assess the activity of ANB020 after single dose administration on clinical scores such as the   Eczema Area EASI), Investigator’s Global Assessment (IGA), Scoring Atopic Dermatitis (SCORAD), Dermatology Quality of Life Index (DLQI), 5D Itch Score, and use of topical corticosteroids in patients with moderate to severe AD from Day 64 to Day 148 after administration of the IP. | | | |
| **Methodology:**  This will be a proof of concept study aiming to assess the effects of ANB020 compared to placebo in patients with AD following saline and HDM skin challenge.  This study will also assess the safety and tolerability of ANB020 in patients with severe to moderate AD. The | | | |

|  |  |
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| effects of ANB020 after saline and HDM skin challenge on the levels of cytokines and accumulation of leukocytes within the interstitial fluid of the HDM challenged areas will be evaluated. The effects of ANB020 on severe to moderate AD will be monitored over a period of 20 weeks.  Patients will present to the clinical facility on Day 1. After verification that all inclusion and no exclusion criteria have been met, the patients will be assigned an enrolment number. On Day 1, blood samples will be collected to assess the patient’s anti-drug antibody (ADA), ex vivo induced IFN-γ levels, as well as serum cytokines; and the patient will receive one dose of placebo. On Day 4, the patients will return to the center for the skin challenge with saline and 0.05 Ig HDM, and the challenge sites will be assessed after 30 minutes. Approximately 1 hour after the HDM skin challenge, suction blister cups will be applied to the site of injection with a vacuum pressure of 250-450 mmHg for 60 to 90 minutes to generate a blister. On Day 5 (within 24 hours of the skin challenge), the patients will return to the study center, the challenge sites will be assessed and cytokine and cellular infiltrate will be obtained by aspiration of blister/interstitial fluid, and safety and observational assessments will occur. On Day 8, the patients, who had a positive response to the HDM skin challenge, will return to the study center to receive one 300 mg IV dose of ANB020, and to have safety, PK, and other assessments performed. The patients may be discharged home following the 6-hour post-dose assessments and with the Investigator’s approval. On Day 11, the patients will return to the study center for the skin challenge with saline and 0.05 Ig HDM and the challenge sites will be assessed after 30 minutes. Approximately 1 hour after the HDM skin challenge, suction blister cups will be applied to the site of injection with a vacuum pressure of 250-450 mmHg for 60 to 90 minutes to generate a blister. Blood samples will be collected to assess ADA, ex vivo induced IFN-γ levels, as well as serum cytokines and PK samples will be obtained. On Day 12 (within 24 hours of the skin challenge), the patients will return to the study center, the challenge sites will be assessed, cytokine and cellular infiltrate will be obtained by aspiration of blister/interstitial fluid, and PK, safety and other assessments be performed. During the 20-week follow-up period, changes in AD disease will be monitored. Blood samples will be collected to assess ADA, ex vivo induced IFN-γ levels, as well as serum cytokines on Day 64, 120, and 148. The patients will be contacted via phone by study staff on Day 29, 43, 50, 57, and 99 and will return to the study center for evaluation visits on Day 15, 22, 36, 64, 85, 120, and End of Study (EOS) visit on Day 148.  Safety and PK assessments will be performed during the study. Patients with any ongoing adverse events (AEs) or serious adverse events (SAEs) at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant by the Investigator. | |
| **Planned number of patients:** | 12 |
| **Diagnosis and main criteria for inclusion:** | Male or female patients (women of childbearing potential must be taking highly effective contraceptive measures) aged >18 years diagnosed with moderate to severe AD based on the Hanifin/Rajka criteria. |
| **Test product, dose and mode of administration:** | ANB020 is an IgG1/kappa monoclonal antibody that specifically neutralizes the biological effects of human interleukin-33 (hIL-33). A dose of 300 mg will be administered by IV infusion in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with 0.9% NaCl. |
| **Placebo, dose, and mode of administration:** | A total of 100 mL placebo (0.9% NaCl) will be administered intravenously on Day 1. |
| **Criteria for evaluation:**  Primary Pharmacodynamic Endpoints:   * Cytokine in blister fluid after HDM skin challenge, including, but not limited to IL-4, IL-5, IL-13, and IL-33. * Differential WBC counts will be measured to monitor peripheral cell populations. Secondary Efficacy Endpoints: | |

|  |
| --- |
| * Urticarial manifestation 0.5 hours after HDM skin challenge between placebo and ANB020. * Circulating cytokines including, but not limited to IL-4, IL-5, IL-13, IL-33, and sST2.  Clinical scores for EASI, IGA, SCORAD, DLQI, and 5D Itch Score.  Patient diary data of corticosteroid usage. Exploratory Pharmacodynamic Endpoints: * Reduction of leukocytes accumulation within interstitial fluid.   Pharmacokinetic Endpoints:  A limited sampling strategy to collect samples of whole blood will be implemented for the determination of ANB020 in human serum for PK assessment. Where possible, the following PK parameters will be determined for ANB020 after a single IV infusion:   * Maximum observed concentration * Time to maximum observed concentration Primary Safety and Tolerability Endpoints: * Assessment of AEs * Measure ANB020 inhibition of cytokine release (IFN-γ) in an ex vivo test * Immunogenicity to ANB020 ADA * Potentially significant and clinically important AEs, SAEs, AEs of special interests, and AEs leading to withdrawal * Physical examinations * Vital signs * Clinical safety laboratory tests (hematology, biochemistry, and urinalysis) * Electrocardiogram (ECG) |
| **Statistical methods:**  For primary and secondary continuous endpoints, change from baseline will be evaluated where possible. Actual and change in data from baseline will be summarized descriptively for each treatment. Mixed-effect analysis of covariance will be used to assess treatment effects. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 or with 2-sided 95% confidence intervals (CIs).  For safety and tolerability, AEs, SAEs, vital signs, physical examinations, ECGs, 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 by preferred term and system organ class of the current Medical Dictionary for Regulatory Authorities (MedDRA) dictionary. Individual listings of all SAEs and AEs leading to discontinuation from the investigational product will be summarized using the current MedDRA dictionary. Similar analyses will be performed for potential significance and clinical importance AEs.  Summaries and listings of data for vital signs, hematology, clinical chemistry and urinalysis laboratory tests, 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. Baseline will be the last assessment before dose. Observed ex vivo induced IFN-γ levels and ADA levels will be summarized with descriptive statistics.  The PK of ANB020 will be evaluated by assessment of drug concentrations in serum. These drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. The PK parameters will be summarized using appropriate descriptive statistics.  For the quantitative efficacy variables, descriptive statistics (including n, mean, minimum, maximum, and 95% CI) will be presented. Corticosteroid usage and urticarious will be summarized with number and percentage of patients. |

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# 1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
| AD | Atopic dermatitis |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ADA | Anti-drug antibody |
| ANCOVA | Analysis of covariance |
| AUC0-inf | Area under the concentration-time curve from time 0 extrapolated to infinity |
| AUC0-last | Area under the concentration-time curve from time 0 to the last quantifiable data point |
| BMI | Body mass index |
| BP | Blood pressure |
| CI | Confidence interval |
| CL | Total clearance |
| Cmax | Maximum observed concentration |
| CV | Coefficient of variation |
| DLQI | Dermatology Quality of Life Index |
| EASI | Eczema Area Severity Index |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EOS | End of Study |
| ET | End of Treatment |
| GMP | Good Manufacturing Practice |
| HDM | House dust mite |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |

|  |  |
| --- | --- |
| IFN-γ | Interferon-Gamma |
| IGA | Investigator’s Global Assessment |
| IL | Interleukin |
| ILC2 | Group 2 innate lymphoid cells |
| IP | Investigational product |
| IUD | Intrauterine device |
| IV | Intravenous |
| mAb | Monoclonal antibody |
| MAD | Multiple ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| n | Sample size or number of observations |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PI | Principal Investigator |
| SAD | Single ascending dose |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SCORAD | Scoring Atopic Dermatitis |
| SOP | Standard operating procedures |
| t1/2 | Terminal half-life |
| tmax | Time to maximum observed concentration |
| WBC | White blood cell |
| WOCBP | Women of child bearing potential |

# 2.0 INTRODUCTION

ANB020 is a first-in-class, anti-interleukin-33 therapeutic antibody to treat T helper-2 (Th2) cell driven inflammatory diseases with underlying interleukin-33 (IL-33) dysregulation. ANB020 is a humanized immunoglobulin subtype G1/kappa (IgG1/kappa) monoclonal antibody (mAb) that specifically neutralizes the biological effects of human interleukin-33 (hIL-33). Interleukin-33, a member of the IL-1 superfamily,1 is a multifunctional cytokine that plays an important role in Th2-mediated cellular immunity and in the pathogenesis of atopic diseases.2,3 ANB020 binds to and inhibits the interaction of IL-33 with its specific cell-surface receptor (ST2) thereby blocking IL-33-driven downstream signalling and subsequent cellular responses. It is being developed for the treatment of atopic diseases such as asthma, atopic dermatitis (AD), and food allergies.

## 2.1 Background Information

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 and IgE-mediated sensitization to food and environmental allergens.5 The etiology of AD is not entirely understood but environmental factors (allergens) trigger in individuals with a genetic predisposition, an immunologic pathogenic cascade leading to disease manifestation. Atopic dermatitis is often associated with, or a prelude, the development of asthma and other allergic diseases. The combination of these conditions and their interleaved progression has been defined 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 indicate 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. The majority of patients achieve disease control with these standard non-systemic treatments. However, there is a significant need for new effective systemic therapies to treat patients with an aggressive form of AD.

Biologics such as mAbs have been considered for the treatment of patients with severe AD. Dupilumab, a mAb, which 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. This is encouraging for the development of ANB020 which targets IL-33, upstream of IL-4, IL-13, and other Th2 cytokines.

This would offer an additional treatment approach to this disease where there remains a need for novel effective therapies.

##### Non-clinical studies

ANB020 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. Non-clinical data obtained from studies with ANB020 in primary human and cynomolgus monkey cells and from *in vivo* non-human primate studies demonstrated that:

* ANB020 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, from peripheral blood mononuclear cells and human whole blood, ANB020 inhibited IL-33-induced interferon-gamma (IFN-γ) production. In human basophils, ANB020 also inhibited IL-33-induced IL-5 production.
* The observed serum half-life (T1/2) of ANB020 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 pharmacokinetic (PK) characteristics for a human IgG1 scaffold monoclonal antibody in the monkey.
* A multiple-dose, GLP-compliant toxicology and toxicokinetic study (4-week duration with an 8-week recovery phase) has been conducted with ANB020 administered by SC and IV injection to cynomolgus monkeys. This study produced no significant test article-related effects and established a No Observed Adverse Effect Level of 50 mg/kg.

These data, together with non-clinical safety data generated, supported a strong scientific rationale for advancing ANB020 into clinical development.

##### Clinical studies

A first-in-man Phase I study (ANB020-001) in healthy subjects has been performed. The single ascending dose (SAD) portion of the study has been completed. In total, 64 subjects were enrolled and dosed (n=32 SC route, n=32 IV route). No change in vitals (blood pressure [BP], heart rate [HR], electrocardiogram [ECG], or body temperature) was noted. Hematology parameters, such as erythrocytes, white blood cell (WBC) and platelets counts, were all within the normal range and did not show any modification or trend related to ANB020 administration. Serum chemistry results were also all in the normal range. A total of 81% subjects in the placebo group and 79% subjects in the ANB020 group had at least one treatment-emergent adverse event (TEAE) during the study. The most commonly reported TEAEs were of mild to moderate intensity and by preferred term were upper respiratory tract infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (32% versus 27% in placebo and ANB020 group, respectively). The PK data from the study has been utilized to determine route and dose to be used in this study. The PK data generated to indicate that a linear PK profile is observed upon ANB020 administration regardless of the route. The predicted ANB020 half-life is in the order of 14 days. Results from emergent data will serve as the basis for the route of administration of ANB020 in future studies.

##### Allergen challenge

It has been reported that an allergen challenge can induce Group 2 innate lymphoid cells (ILC2) infiltration into human and mouse skin. House dust mite (HDM) extract is one of the most common aeroallergens that are associated with an exacerbation of AD symptoms.6 To examine ILC2 recruitment to allergen-provoked skin, suction blisters were used to sample skin cells before and after HDM allergen delivery in the epidermis of humans. The cells infiltrating the blister were extracted 26 hours after intra-epidermal administration of HDM extract to the skin. After HDM administration, there was a statistically significant infiltration into the blisters from allergic individuals compared with non-allergic individuals for granulocytes, monocytes, and lymphoid cells. The infiltrating lymphoid cells included CD3, CD56, and ILC2 populations. ILC2s were clearly observed after allergen challenge. Higher concentrations of IL-13, IL-5, and IL-4 were detected in the blister fluid of allergic donors 26 hours after HDM allergen challenge, whereas in non-allergic individuals there were no detectable type 2 cytokines. It was also observed that ST2-expressing ILC2 infiltrated the skin 26 hours after HDM challenge in humans.

## 2.2 Rationale

This proof of concept study is intended to explore the activity of ANB020 in patients with AD after HDM challenge. Only HDM sensitized in patients with AD react to HDM and no response is observed in healthy subjects. Although rapid changes within 24 hours after a challenge are observed only in patients, the degree of response might vary among patients, with some having more pronounced manifestations (i.e., cytokine release in blister fluid). The IL-33 induction and role in HDM challenge has been demonstrated in several studies. No response was observed in patients treated with 0.9% NaCl. However, the potential benefit of its inhibition has never been tested in patients. The primary as well as secondary exploratory endpoints will be based on reduction of cytokine and white cells in blister fluid after HDM skin challenge. Therefore, to quantitatively compare results generated in the presence of ANB020, each patient will be first challenged with HDM under placebo conditions. These conditions will serve as a baseline in each patient to compare data generated by the HDM challenge under the ANB020 treatment.

After ANB020 administration, the patients will be monitored for a period of 20 weeks.

## 2.3 Hypothesis

This is an exploratory study and no hypothesis testing will be performed.

## 2.4 Risk-Benefit Assessment

A patient with AD may or may not benefit from participating in this study. Based upon the inhibition of IL-33 by the investigational product (IP) and pre-clinical study results, patients with AD may benefit. Participation in this study may help develop important scientific knowledge that could contribute to the development of a new medication and better treatment of patients who suffer from AD, asthma, and food allergies.

ANB020 has been extensively tested in animals and was found to be safe and well tolerated in a Phase I SAD study (ANB020-001) in healthy subjects. In animal studies, there were no ANB020 related adverse events (AEs) or abnormal ECG findings and the administration of ANB020 had no effect on hematology, coagulation, clinical chemistry, or urinalysis test results. In this study, 64 healthy subjects were enrolled and dosed. No change in vitals (BP, HR, ECG, or body temperature) was noted. Hematology parameters, such as erythrocytes, WBC and platelets counts, were all within the normal range except one volunteer in the 750 mg dose group. All others did not show any modification or trend related to ANB020 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 ANB020 group had at least one treatment-emergent adverse event (TEAE) during the study. The most commonly reported TEAEs were of mild to moderate intensity and by preferred term were upper respiratory tract infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (32% versus 27% in placebo and ANB020 group, respectively). No AEs were deemed by the Principal Investigator (PI) to be related to ANB020. 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 study completion with no sequelae. No other observations of decreased neutrophils were observed. No dose dependent AE presentation was reported.

Although nothing in the testing of ANB020 to date indicates that an allergic reaction is likely, a reaction to any drug 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 pulse, or sweating.

As ANB020 is a monoclonal antibody, based on clinical studies with other monoclonal antibodies, study participants may experience symptoms of an apparent allergic reaction to the drug, also known as ‘cytokine release syndrome’. The symptoms of this vary dramatically but can include:

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

# 3.0 STUDY OBJECTIVES

## 3.1 Primary Objectives

The primary objectives of the study are as follows:

* To measure the decrease of cytokines within the interstitial fluid (where saline and HDM had been administered), in patients receiving ANB020 compared to placebo.
* To assess the effect of ANB020 on differential WBC counts.
* To assess the safety and tolerability of single dose administration of ANB020 in patients with AD.

## 3.2 Secondary Objectives

The secondary objectives of the study are as follows:

* To assess the effect of ANB020 on serum cytokines.
* To compare the changes in urticarial manifestation 0.5 hours after HDM challenge between patients receiving placebo and then ANB020.
* To describe the limited PK of ANB020 following a single, IV dose.
* To assess the ex vivo PD activity of ANB020 on IFN-γ levels.
* To test for any immunogenicity to ANB020.

## 3.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

* To assess the effect of ANB020 on leukocytes within the interstitial fluid.
* To assess the activity of ANB020 after single dose administration on clinical scores such as the Eczema Area Severity Index (EASI), Investigator’s Global Assessment (IGA), Scoring Atopic Dermatitis (SCORAD), Dermatology Quality of Life Index (DLQI), 5D Itch Score, and use of topical corticosteroids in patients with moderate to severe AD from Day 64 to Day 148 after administration of the IP.

# 4.0 INVESTIGATIONAL PLAN

## 4.1 Summary of Study Design

This is a Phase II proof of concept placebo-controlled study to investigate ANB020 activity upon HDM skin challenge in approximately 12 patients suffering from moderate to severe AD at a single center in the United Kingdom. The study will also assess the safety and tolerability of ANB020 in patients with moderate to severe AD.

Patients will present to the clinical facility for the Day 1 outpatient visit. After verification that all inclusion and no exclusion criteria have been met, the patients will be assigned an enrolment number. On Day 1, blood samples will be collected to assess anti-drug antibody (ADA), ex vivo induced IFN-γ levels, as well as serum cytokines; and the patient will receive one IV dose of placebo on Day 1. On the Day 4 outpatient visit, the patients will return to the study center for the skin challenge with saline and 0.05 Ig HDM to be performed. The skin challenge site will be assessed after 30 minutes. Approximately 1 hour after the HDM skin challenge, suction blister cups will be applied to the site of injection with a vacuum pressure of 250-450 mmHg for 60 to 90 minutes to generate a blister. On Day 5 (within 24 hours of the skin challenge), the patients will return to the study center, the challenge sites will be assessed and cytokine and cellular infiltrate will be obtained by aspiration of blister/interstitial fluid, and safety and other assessments be performed. On Day 8, the patients who had a positive response to the HDM skin challenge, will return to the study center to receive one IV dose of ANB020, and to have the safety, PK, and other assessments performed. The patients may be sent home following the 6-hour post-dose assessments and with the Investigator’s approval. On the Day 11 outpatient visit, the patients will return to the study center for the skin challenge with saline and 0.05 Ig HDM and the challenge sites will be assessed after 30 minutes. Approximately 1 hour after the HDM skin challenge, suction blister cups will be applied to the site of injection with a vacuum pressure of 250–450 mmHg for 60 to 90 minutes to generate a blister. Blood samples will be collected to assess ADA, ex vivo induced IFN-γ levels, as well as serum cytokines and PK samples will be obtained. On Day 12 (within 24 hours of the skin challenge), the patients will return to the study center for an outpatient visit, the challenge sites will be assessed, cytokine and cellular infiltrate will be obtained by aspiration of blister/interstitial fluid, and PK, safety and other assessments be performed. During the 20-week follow-up period, changes in AD disease will be monitored. Blood samples will be collected to assess ADA, ex vivo induced IFN-γ levels, as well as serum cytokines on Day 64, 120, and 148. Patients will be contacted via phone by study staff on Day 29, 43, 50, 57, and 99 and will return for outpatient visits to the study center for evaluation on Day 15, 22, 36, 64, 85, 120, and End of Study (EOS) visit on Day 148. The study design is presented in Figure 1.

Figure 1 Schematic of Study Design for Protocol ANB020-002

Screening Visit (7

-

14

days

prior to Day

1)

Placebo (Day

1)

(n=12)

HDM

s

kin

challenge

assessment (Day

4

)

(n=12)

Cytokine and cellular infiltrate will be obtained and evaluated

with

safety and

other

assessments

within 24 hours

(

Day

5)

(n=12)

HDM

skin challenge

assessment (Day

11

)

(n=12)

T

elephonic Interview (Day

,

29

99

, 50, 57, and

43

)

(n=12)

Study center assessment visits

Day

(

22

15

,

,

36

, 64,

85

, 120,

and

EOS/ET visit)

(n=12)

Phase II

Study of m

ale and

female

patients >18

years

diagnosed with

AD

ANB020 (Day

8

)

(n=12)

Cytokine and cellular infiltrate will be obtained and evaluated

with

safety and

o

ther

assessments

within 24 hours

Day

(

12

)

(n=12)

Abbreviations: AD = atopic dermatitis; EOS = End of Study; ET = End of Treatment; HDM = house dust mite; n=sample size

Protocol Number: ANB020-002 ANB020

##### Table 4.1 Schedule of Events

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Placebo Dosing** | | | **ANB020 Dosing** | | | |  |  |  |  | | | | | | | | |
| **Assessment Days** | **Screening**  ***7-14 days prior to***  ***D1*** | **Day**  **1** | **Day**  **4** | **Day**  **5** | **Day 8** | **Day 11** | **Day 12** | **Day 15**  **(study center)** | **Day**  **22c**  **(study center)** | **Day**  **29c**  **(T)** | **Day**  **36c**  **(study center)** | **Day**  **43c**  **(T)** | **Day**  **50c**  **(T)** | **Day 57c**  **(T)** | **Day 64**  **(study center)** | **Day 85**  **(study center)** | **Day 99**  **(T)** | **Day 120**  **(study center)** | **End of**  **Study**  **Day 148**  **(study center)** | **Early termination**  **visit** |
| **General**  **Assessments** |  | | | | | | | | |  |  |  | | | | | | | | |
| Informed Consent | X | Xa |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HDM Challenge Skin Assessmentf | Xe |  | X |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EASI, IGA, SCORAD, DLQI, 5D Itch Score, corticosteroid usage | X | X |  |  | X |  |  | X | X |  | X |  |  |  | X | X |  | X | X | X |
| Patient diary | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Safety Assessments** |  | | | | | | | | |  |  |  | | | | | | | | |
| Physical examination | X | X |  |  | X |  |  | X |  |  |  |  |  |  |  |  |  |  | X | X |
| Safety laboratory testing | X | X |  |  | X |  |  | Xd | Xd |  | Xd |  |  |  | X | X |  |  | X | X |
| Whole blood sampling for ex vivo induced IFN-γ |  | X |  |  |  | X |  |  |  |  |  |  |  |  | X |  |  | X | X | X |
| Serum sampling for  ADA |  | X |  |  |  | X |  |  |  |  |  |  |  |  | X |  |  | X | X | X |
| Virology, TB screening, and Drugs of abuse | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vital signs | X | X |  |  | X |  |  | X | X |  | X |  |  |  | X | X |  | X | X | X |

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|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Placebo Dosing** | | | **ANB020 Dosing** | | | |  |  |  |  | | | | | | | | |
| **Assessment Days** | **Screening**  ***7-14 days prior to***  ***D1*** | **Day**  **1** | **Day**  **4** | **Day**  **5** | **Day 8** | **Day 11** | **Day 12** | **Day 15**  **(study center)** | **Day**  **22c**  **(study center)** | **Day**  **29c**  **(T)** | **Day**  **36c**  **(study center)** | **Day**  **43c**  **(T)** | **Day**  **50c**  **(T)** | **Day 57c**  **(T)** | **Day 64**  **(study center)** | **Day 85**  **(study center)** | **Day 99**  **(T)** | **Day 120**  **(study center)** | **End of**  **Study**  **Day 148**  **(study center)** | **Early termination**  **visit** |
| Urinalysis | X | X |  |  | X |  |  | X | X |  | X |  |  |  | X | X |  |  | X | X |
| Pregnancy test (WOCBP only) | X | X |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X | X |
| 12-Lead ECG | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **PK/PD Assessments** | | | | | | | | | |  |  |  | | | | | | | | |
| Samples for PKb |  |  |  |  | X | X | X |  |  |  |  |  |  |  | X |  |  | X | X | X |
| Interstitial Fluid sampling for PD leukocytes & cytokines |  |  |  | X |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum sampling for PD cytokinesb and sST2 |  | X |  | X | X |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Dosing** | | | | | | | | | |  |  |  | | | | | | | | |
| Placebo |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ANB020 |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HDM Skin Challenge | Xe |  | X |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Abbreviations: ADA = Anti-drug Antibody, EASI = Eczema Area Severity Index, DLQI = Dermatology Quality of Life Index; ECG = electrocardiogram; HDM = house dust mite; IFN-γ = Interferon-Gamma, IGA = Investigator Global Assessment; PK = pharmacokinetics; PD = pharmacodynamics; SCORAD = Scoring Atopic Dermatitis; sST2 = soluble ST2; T = Telephonic interview; TB = tuberculosis; WOCBP = Women of childbearing potential a Confirm informed consent and continued willingness to participate.

1. See Section 1.0 (Appendix 2) for schedule of PK and PD collection time points.

1. Staff at centers will conduct telephone interview (T) with the patient on Days 29, 43, 50, 57, and 99 for patient diary, corticosteroid usage, AEs, and concomitant medications. Patients will return to study center for study center assessment visits on Days 15, 22, 36, 64, 85, 120 and 148/EOS or ET for patient diary review, corticosteroid usage, EASI, IGA, SCORAD, DLQI, and 5D Itch Score. d See Table 7.1 for clinical laboratory parameters. e If HDM positive response has been recorded within 3 months of screening date, HDM skin challenge does not need to be conducted at the screening visit. f30 minutes after the administration

Patient diary: Patient diary can capture daily topical corticosteroid use, AEs, and concomitant medications from Screening through Day 64 and weekly from Day 65 through Day 148.

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ANB020

## 4.2 Discussion of Study Design

ANB020, a first-in-class, anti-IL-33 therapeutic antibody developed by AnaptysBio, 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 non-clinical and clinical studies, justifying its further development in patients with AD. Emergent data of the Phase I study (ANB020-001) are the basis for the dose and IV route of administration of ANB020. The 300 mg IV dose was found to be safe and well tolerated in healthy subjects. In this SAD/multiple ascending dose (MAD) Phase I study in healthy subjects, the SAD portion of the study has been completed but the MAD portion of the study is ongoing. In the SAD portion of the study, 64 subjects were enrolled and dosed. No change in vitals (BP, HR, ECG, or body temperature) was noted. Hematology parameters, such as erythrocytes, WBC and platelets counts, were all within the normal range except one volunteer in the 750 mg dose group. All others did not show any modification or trend related to

ANB020 administration. Serum chemistry results were also all in the normal range. A total of 81% subjects in the placebo group and 79% subjects in the ANB020 group had at least one treatment-emergent adverse event (TEAE) during the study. The most commonly reported TEAEs were of mild to moderate intensity and by preferred term were upper respiratory tract infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (32% versus 27% in placebo and ANB020 group, respectively). No AEs were deemed by the PI to be related to ANB020. 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 study completion with no sequelae. No other observations of decreased neutrophils were observed. No dose dependent AE presentation was reported.

The dose of ANB020 selected for this study has provided complete inhibition of IL-33 induced cytokine release and has been dosed safely in study ANB020-001.

Patients 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 patients, but they can have significant side effects. The use of more targeted immune modulators such as ANB020 can 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 is a proof of concept study7 aiming to assess the effects of ANB020 compared to placebo in patients with AD and provide evidence that the hypothesized mechanism is affected by the IP and that the effect on the mechanism leads to a desired short-term clinical outcome.

This study uses a placebo to obtain baseline assessments to allow patients to serve as their own controls for the assessments performed after ANB020 administration. All patients will receive active ANB020 on Day 8 of the study. The half-life of ANB020 was approximately 2 weeks in Phase I studies in healthy subjects. Following patients for 4.6 months after ANB020 administration will allow time for PK, PD, and safety assessments from a single dose.

## 4.3 Selection of Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the patients included in the study and that the results of the study can be used. It is imperative that patients fully meet all of the inclusion criteria and none of the exclusion criteria.

### 4.3.1 Inclusion Criteria

Patients will be enrolled in the study only if they meet all of the following criteria:

* Male and female patients with age >18 years and able to give informed consent.
* Patients with a confirmed clinical diagnosis of AD based on the Hanifin/Rajka criteria (Section 13.0).
* The EASI score ≥14 at screening to reflect moderate to severe.
* Patients with a confirmed positive response to a skin HDM challenge.
* Body mass index (BMI) of 18 to 32 kg/m2 (inclusive) and total body weight >50 kg (110 lb). BMI = weight (kg)/(height [m2]).
* Willing and able to comply with the study protocol requirements, in the Investigator’s opinion, including applying topical corticosteroid ointment and emollient as specified by the protocol.
* Have the ability to read and understand the study procedures and have the ability to communicate meaningfully with the Investigator and staff.
* Female patients of childbearing potential must have a negative pregnancy test at screening and Day 1, must not be lactating, or intend to become pregnant during the study period, and be surgically sterile or postmenopausal or using highly effective methods of contraception throughout the study and for 20 weeks after the last dose of the IP. Postmenopausal patients defined as 1) aged over 45 years with at least 1 year of amenorrhea and levels of follicle stimulating hormone over 20 UI/L or 2) aged over 50 years with at least 1 year of amenorrhea. Male patients must be willing to use contraception throughout the study and for 20 weeks after the last dose of IP which

includes a total of 5 half-lives of the study drug (estimated to be around 95 days) plus an additional 50 days (which includes the duration of sperm turnover) post-treatment completion.

### 4.3.2 Exclusion Criteria

Patients will not be enrolled in the study if they meet any of the exclusion criteria:

* Have concomitant dermatological or medical condition(s) which may interfere with the Investigator’s ability to evaluate the patient's response to the IP.
* Have applied any topical medication (including corticosteroids, calcineurin inhibitor, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) or herbal preparation to the area selected for treatment within 14 days before screening.
* Have received antibiotic treatment within 2 weeks before screening.
* Have received systemic treatment for AD (including systemic corticosteroids, non-steroidals, immunosuppressants or immunomodulating drugs, antihistamines, or treatment with light or use of a tanning booth) within 4 weeks before screening.
* Have received any investigational drug or been part of any interventional clinical study within a period of 3 months or 5 half-lives (whichever is longer) before screening.
* Have a history of hypersensitivity or allergic reactions to polysorbate 80 a component of ANB020 formulation or the inactive ingredients (excipients).
* Have a history of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.
* History of drug, alcohol or other substance abuse, or other factors limiting the ability to cooperate and to comply with the study protocol.
* Hypersensitivity to topical corticosteroid or to any other ingredients contained in the topical corticosteroid product used in the study.
* Use of any over-the-counter or complementary medicines, within 7 days before screening.
* Clinical diagnosis of bacterial infections of the skin, including impetigo or abscesses which meet any of the following criteria: hospital admission within 4 weeks of screening; received IV, oral or topical antibiotics within 2 weeks of screening.
* Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV 1 and 2 antibodies.
* Have any other physical, mental, or medical conditions which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
* History of parasitic infections within 12 months before screening.
* Receipt of a live attenuated vaccine within 4 weeks before screening.
* Planned surgery during the study.
* History of malignancy within 5 years, except non-melanoma skin cancer which has been fully treated with no current active disease.

### 4.3.3 Disease Diagnostic Criteria

Hanifin and Rajka AD diagnostic criteria require the presence of 3 or more out of 4 basic and 3 or more out of 23 minor criteria. These criteria are found in Section 13.0.

### 4.3.4 Patient Restrictions

The following restrictions may affect patient participation in this study:

* Availability to attend visits according to the protocol.
* Concomitant medication restrictions as described in Section 0.
* Fasting for 8-10 hours prior to visits which include routine safety laboratory assessments.
* Restricted alcohol intake (<28 units per week).
* Strenuous exercise should be avoided up to 72 hours before planned study visits.
* Woman of child-bearing potential (WOCBP) must use a highly effective method of contraception during the study period and/or for at least 20 weeks following the last dose of IP. Male patients must be willing to use contraception throughout the study and for 20 weeks after the last dose of IP which includes a total of 5 half-lives of the study drug (estimated to be around 95 days) plus an additional 50 days (which includes the duration of sperm turnover) post treatment completion.

At a minimum, patients must agree to the use of one method of highly effective contraception as listed below:

**Highly effective methods of contraception**

* Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP patient or male patient’s WOCBP partner. Female partners of male patients participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug i.e. IUDs, such as ParaGard®.  Tubal ligation
* Vasectomy

Acceptable alternate methods of highly effective contraception must be discussed with the PI to ensure highly effective methods of contraception are instituted prior to patient receiving any dose of IP.

**Less effective methods of contraception**

* Diaphragm
* Cervical cap
* Vaginal sponge
* Male Condom\*
* Progestin only pills by male patient’s WOCBP partner  Female Condom\*

\*A male and female condom must not be used together Patient Withdrawal

All patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study. AnaptysBio and Quintiles must be contacted, and if the patient has received a dose of placebo or ANB020, the patient must be followed up until EOT (Day 148) for any AEs and/or serious adverse events (SAEs).

In addition, patients will be withdrawn from the IP and from the study in the following circumstances:

* The Investigator decides that the patient should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, appropriate measures are to be taken. AnaptysBio and/or Quintiles is to be notified immediately.
* The patient is unwilling to continue in the study.
* Lack of compliance with protocol.
* The Investigator or AnaptysBio, for any reason, stops the study.
* If a female patient becomes pregnant.
* New information suggests taking part in the study may not be in the patient’s best interest.

Patients who discontinue the study early will have early termination procedures performed as shown in the Table 4.1. Patients who are withdrawn from the study, post Day 12 assessments, will not be replaced. Patients who discontinue prior to completing the Day 12 assessments may be replaced.

# 5.0 STUDY TREATMENTS

## 5.1 Treatments Administered

ANB020 is a humanized IgG1/kappa monoclonal antibody (mAb) and 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)-XELTM system to achieve a desired functional inhibitory potency.

ANB020 may be administered to patients by IV infusion in polyvinyl chloride or polyolefin bags following dilution with sterile normal saline (0.9% NaCl) in 100 mL. Placebo may be administered by IV infusion with sterile normal saline (0.9% NaCl) in 100 mL. Infusions will be administered over 1 hour.

Patients will also be supplied with a topical corticosteroid cream to use for the AD during the study and are to avoid other topical medicated treatments for AD. See Section 5.8.2.

## 5.2 Identity of Investigational Product

ANB020 investigational product for SC or IV injection is manufactured by Patheon of

Greeneville, NC., USA under Good Manufacturing Practice (cGMP) regulations. ANB020 drug product is provided as a sterile clear solution in a glass vial for IV infusion and contains no preservatives.

ANB020 vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. The placebo contains no active drug and will be sterile normal saline (0.9% NaCl) for injection. The center will procure the placebo from the pharmacy stock supply. ANB020 vials may be stored at room temperature (>8°C to 25°C [46°F to 77°F]) in the undiluted and/or diluted state for up to 8 hours. The vials should remain in the bulk cartons during storage and until use to provide protection from light. Vial contents should not be frozen or shaken. They are intended for singleuse only; therefore, any remaining solution should be discarded.

Table 5.1 provides an outline of the dosing schedule for the study.

##### Table 5.1 Dosing Schedule

|  |  |  |
| --- | --- | --- |
| **Investigational product** | **Dosage form and strength** | **Manufacturer** |
| ANB020 | IV infusion: 300 mg/100 mL once on Day 8 | Patheon |

Abbreviation: IV = intravenous

## 5.3 Packaging and Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines.

All IPs should be kept in a secure place under appropriate storage conditions. The IP label on the packaging specifies the appropriate storage.

## 5.4 Method of Assigning Patients to Treatment Group

This is a proof of concept study devoid of any randomization schedule and patients are not blinded to treatment assignment of ANB020 or placebo. Once the patient meets inclusion and exclusion criteria and has provided an informed consent, they will be assigned to placebo and then the IP for a single injection of each.

## 5.5 Selection of Doses in the Study

ANB020 will be administered as a single IV dose of 300 mg/100 mL and placebo as 100 mL NaCl.

The dose of ANB020 selected for this study has provided complete inhibition of IL-33 induced cytokine release and has been dosed safely in Study ANB020-001.

## 5.6 Selection and Timing of Dose for Each Patient

All patients will receive the same dose of placebo and ANB020. The infusion will be administered at the rate of 100 mL per hours via a Baxter infusion solutions set (FNC2110; prime volume 16 mL) or equivalent followed by a 16 mL IV saline flush, at the same infusion rate, to ensure that no residual drug remains in the infusion line. No in-line filter is to be used. The ANB020 or placebo infusion may be slowed or interrupted for patients experiencing infusion-related AEs.

## 5.7 Blinding

Site staff and patients will not be blinded to study drug administration (ANB020 or placebo).

## 5.8 Prior and Concomitant Treatments

### 5.8.1 Excluded Medications

The following medications will not be permitted during the study. Use of these excluded medications is a protocol violation and should be recorded in the electronic case report form (eCRF). Study supplied rescue medication (topical corticosteroid) and systemic antibiotics for the treatment of a recurrent infection will be allowed during the study.

* Any topical medication (including corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) or herbal preparation to the area selected for treatment within 14 days before screening.
* Any systemic antibiotics within 2 weeks before screening.
* Any systemic treatment for AD (including systemic corticosteroids, immunosuppressants, or immunomodulating drugs, or antihistamines, or treatment with light, or use of a tanning booth) within 4 weeks before screening.
* Any over-the-counter or complementary medicines within 7 days before screening except for paracetamol. Aspirin and non-steroidal anti-inflammatories should be avoided within 7 days before screening, and until after all the blister sampling has been completed.
* Any live attenuated vaccine within 4 weeks of screening and for the duration of the study (Day 148) or for 140 days post last dose of IP.

### 5.8.2 Allowed Medications

Throughout the treatment period, patients will continue to apply own emollient at least once daily to all dry areas, and Mometasone Furoate 0.1% cream once per day to all active skin lesions on the body. For lesions affecting the face or flexures, hydrocortisone 2.5% cream may be used. If at any time, in the opinion of the PI, it is not in the patient’s best interests to continue this regimen, the frequency or potency of topical corticosteroid may be decreased without discontinuing the study. The reason for modification of the topical regimen must be entered into the eCRF. The patient should be returned to using the protocol specified topical regimen as soon as the PI believes it is safe to do so. An escalation in therapy is allowed at any time, if, in the opinion of the PI, it is required for adequate treatment of the patient’s AD. The reason for the escalation in therapy must be recorded in the eCRF. If the patient requires an escalation in topical corticosteroid therapy (e.g. a higher potency topical corticosteroid) the patient should remain in the study. The patient should return to using the protocol-specified topical regimen as soon as the PI believes it is safe to do so.

The emollient and topical corticosteroid will be supplied by the local hospital pharmacy as part of patient’s ongoing medical care.

The topical corticosteroid should not be applied to the upper inner arms during the screening period and until 48 hours after administration of anti-IL-33.

Females of childbearing potential are to continue using their hormonal contraceptives.

The Investigator must record the use of all concomitant medications, both prescribed and over the counter, into the eCRF and patient’s medical records. This includes medications used on both a regular and an as needed basis. Patients 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.

## 5.9 Medical Care of Patients after End of Study

All patients will return to the study center on EOS (Day 148) or ET visit for final safety and EOS assessments. After this time, patients should be treated according to the Investigator’s clinical judgment. Care after EOS/ET will not be provided by AnaptysBio. Any significant AE which in the opinion of the Investigator is related to the IP, SAE, or pregnancy occurring within 140 days of the dose of IP should be reported to safety team of Quintiles and followed up until outcome of event has resolved or a new baseline is established.

## 5.10 Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

## 5.11 Investigational Product Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all the IPs using the Drug Accountability Form. These forms must be available for inspection at any time.

All the IP supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused IP supplies and packaging materials are to be inventoried and returned to Quintiles/AnaptysBio by the Investigator or may be destroyed on site following institutions SOPs and proper accountability by Quintiles site monitor. The Investigator is not permitted to return or destroy unused IP supplies or packaging materials unless authorized by Quintiles.

# 6.0 STUDY PROCEDURES

Study procedures will be performed as detailed in the Schedule of Events in Table 4.1. Assessments scheduled on the day of IP administration must be performed prior to the IP infusion unless otherwise noted. All assessments will be performed on the day of the specified visit but after the Day 22 visit, there is a window of +/-2 days in order to allow for scheduling issues/national holidays, etc.

## 6.1 Screening

Each potential patient will provide informed consent at screening before starting any study related procedures. The eligibility of patients will be determined during the screening period. Screening procedures will be carried out in accordance with the Schedule of Events in Table 4.1.

## 6.2 Study Day Procedures

### 6.2.1 Blood volume

The total blood volume for each patient will not exceed 247 mL or the National Institute of Health allotted amounts of 550 mLin any 8-week period. The blood volume withdrawn during each visit is provided in Table 6.1.

##### Table 6.1 Blood Volume Sampling During Each Visit

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Visits** | **Screening** | **Day 1 Predose** | **Day 5** | **Day 8 Predose** | **Day 8 (0.5H)** | **Day 8 (EOI)** | **Day 8 (EOI 3H)** |
| Total blood volume sampled during each visit (mLs) | 22.5 | 3 | 8.5 | 25.5 | 5 | 5 | 5 |
|  |  |  |  |  |  |  |  |
| **Visits** | **Day 8 (EOI 6H)** | **Day 11** | **Day 12** | **Day 15** | **Day 22** | **Day 36** | **Day 64** |
| Total blood volume sampled during each visit (mLs) | 5 | 16 | 13.5 | 10.5 | 10.5 | 10.5 | 26.5 |
|  |  |  |  |  |  |  |  |
| **Visits** | **Day 85** | **Day 120** | **End of**  **Study**  **Day 148** |  |  |  |  |
| Total blood volume sampled during each visit (mLs) | 10.5 | 16 | 26.5 |  |  |  |  |

Abbreviation: EOI = End of Infusion

### 6.2.2 Saline/HDM Skin Challenge

The HDM extract (saline and 0.05 Ig HDM) will be delivered by intra-epidermal skin prick test to the upper arm of the patients at the screening visit, if a HDM positive response has not been recorded within 3 months of the screening date. A saline control will also be delivered by a separate intra-epidermal skin prick test. An immediate urticarial response of at least 3 mm after 30 minutes will be considered a positive response. The size of the urticarial response 30 minutes after injection will be recorded in the eCRF. The orthogonal diameter of the weal will be measured at the mid-point of the longest axis and the average of the longest and the orthogonal diameter must be calculated. Pseudopodia will not be assessed. The negative control must be <2 mm for the test to be considered valid. If the negative control is >2 mm the test should be repeated on another day.

#### 6.2.2.1 Blister Generation

Approximately 1 hour after the application of the HDM skin challenge, suction blister cups will be applied to the site of injection with a vacuum pressure of 250 to 450 mmHg for 60 to 90 minutes. A non-adherent dressing should be applied to protect the blister site and the patient instructed to avoid any significant exertion or contact that could rupture the blister prior to collection of the interstitial blister fluid.

#### 6.2.2.2 Collection of blister interstitial fluid

Within 24 hours of the HDM skin challenge (Days 5 and 12), blister fluid will be aspirated, after the skin has been prepped with alcohol, with a 30-gauge needle. The blister/interstitial fluid will be processed according to the Laboratory Manual.

### 6.2.3 Assessment of Atopic Dermatitis

Severity of AD from baseline through EOS follow-up will be assessed by the Investigator using the EASI, IGA, SCORAD, DLQI, and 5D Itch Score.

#### 6.2.3.1 Eczema Area and Severity Index

The EASI score will be recorded in the eCRF at the time points indicated in the Schedule of

Events. The EASI instructions and forms are in Section 14.08. The ‘worksheet’ for each visit should be placed in the source documents to allow for monitoring. It is recommended that the same Investigator/Sub-Investigator completes the scale for all time points for a given patient.

#### 6.2.3.2 Investigators Global Assessment

The IGA will be recorded in the eCRF at the time points indicated in the Schedule of Events.

The IGA scale to be used is in Table 6.2. It is recommended that the same

Investigator/Sub-Investigator completes the scale for all time points for a given patient.

##### Table 6.2 Investigators Global Assessment

|  |  |  |
| --- | --- | --- |
| **Grade** | **Severity** | **Findings** |
| 0 | Clear | No inflammatory signs of atopic dermatitis |
| 1 | Almost clear | Just perceptible erythema and just perceptible papulation/infiltration |
| 2 | Mild disease | Mild erythema and mild papulation/infiltration |
| 3 | Moderate disease | Moderate erythema and moderate papulation/infiltration |
| 4 | Severe disease | Severe erythema and severe papulation/infiltration |
| 5 | Very severe disease | Severe erythema and severe papulation/infiltration with oozing/crusting |

Source: Journal of Dermatological Treatment. 2006; 17: 143–150.**9**

#### 6.2.3.3 Severity Scoring of Atopic Dermatitis

The SCORAD index will be calculated per Section 15.0.10,11 Total score and scores for extent of disease, disease severity, and subjective symptoms should be recorded on the eCRF at the time points indicated in the Schedule of Events. The ‘worksheet’ for each visit should be placed in the

source documents to allow for monitoring. It is recommended that the same

Investigator/Sub-Investigator completes the scale for all time points for a given patient.

#### 6.2.3.4 Dermatology Life Quality Index

The patient should complete the DLQI PRO in Section 16.012 at the time points indicated in the Schedule of Events. The DLQI score should be recorded in the eCRF. The ‘worksheet’ for each visit should be placed in the source documents to allow for monitoring.

#### 6.2.3.5 5D Itch Scale

The patient should complete the 5D Itch Scale PRO in Section 16.013 at the time points indicated in the Schedule of Events. The 5D Itch score should be recorded in the eCRF. The ‘worksheet’ for each visit should be placed in the source documents to allow for monitoring.

#### 6.2.3.6 Measurement of topical corticosteroid use

Patients will be dispensed a tube (weight recorded in eCRF) with 80 grams of 0.1% Mometasone Furoate topical corticosteroid cream at Day 1 visit. At each visit thereafter the patient should bring the tube of corticosteroid to allow for weighing of the tube (record in eCRF) to determine the amount of topical corticosteroid cream used since the previous visit. As needed additional tubes may be dispensed at visits (continue to record weights through EOS/ET).

### 6.2.4 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

* The PK samples will be collected at the nominal time.
* All safety assessments will be timed and performed relative to the start of dosing.

### 6.2.5 Discharge from the Study Center

A patient will be allowed to leave the premises following 6 hours after the ANB020 administration at the study center and completion of study-specific procedures providing that:

* No AEs have been reported during the study visit.
* The patient responds in the affirmative when asked if they are feeling well.

If any of these conditions are not met, then the patient will only be allowed to leave the clinical unit with the authorization of the Investigator or appropriately qualified delegate.

# 7.0 SAFETY, PHARMACODYNAMIC, PHARMACOKINETIC,

## AND EFFICACY ASSESSMENTS

## 7.1 Safety

Safety assessments will be based on medical review of AE reports, the results of physical examinations, and clinical laboratory tests. The incidence of observed AEs will be reviewed for potential significance and clinical importance. Patients with any ongoing AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant by the Investigator.

### 7.1.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study (washout, treatment, and follow-up) period.

Definition of AE: An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Definition of SAE: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to the IP or not) that at any dose:

* Results in death.
* Is life-threatening (the patient is at a 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).
* Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
* Results in persistent or significant disability/incapacity.
* Is a congenital abnormality/birth defect.
* Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g. neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An adverse drug reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

##### Severity

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

* Mild events are usually transient and do not interfere with the patient’s daily activities.
* Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
* Severe events interrupt the patient’s usual daily activity.

##### Relationship

The causal relationship between the IP and the AE has to be characterized as unrelated, unlikely, possible, probable or unknown (unable to judge).

Events can be classified as “unrelated” if there is not a reasonable possibility that the IP caused the AE.

An “unlikely” relationship suggests that only a remote connection exists between the IP and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.

A “possible” relationship suggests that the association of the AE with the IP is unknown; however, the AE is not reasonably supported by other conditions.

A “probable” relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator’s clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

All efforts should be made to classify the AE according to the above categories. The category

“unknown” (unable to judge) may be used only if the causality is not assessable, e.g. because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

#### 7.1.1.1 Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the study, treatment or follow-up period, are to be recorded on the appropriate AE pages (either ‘serious’ or

‘non-serious’) in the eCRF. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, relationship to the IP. Each event should be recorded separately.

The ANB020 or placebo infusion may be slowed or interrupted for patients experiencing infusion-related AEs. Following the infusion, all patients will be observed for fever, chills, rigors, hypotension, nausea, or other infusion-related AEs.

All SAEs (as described in Section 7.1.1) that occur after the patient has signed informed consent (including the protocol defined follow-up period), regardless of judged relationship to the study drug, or after the study period, if considered serious and related to IP or to the patient’s participation in the study, must be reported to Quintiles within 24 hours of the Investigator’s knowledge of the event. The SAE reporting will originate in the electronic data capture (EDC) system and an email will be sent to the designated responsible parties defined in the Safety Plan. The paper SAE form is in place as a back-up in the rare event that EDC is not accessible to the reporter of the SAE and the paper SAE form should be sent to ***QLS\_Anaptys@quintiles.com.***

The following documents should be submitted to Quintiles Safety:

* Serious Adverse Event Report Form.
* The following eCRFs or de-identified source documents:
  + Demographics page(s) o Medical history page(s) o Adverse event page(s) o Concomitant medication page(s)
  + Hospital discharge summary: If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge.

Following are Investigator responsibilities:

* Record diagnosis instead of signs and symptoms when available using accepted medical terminology.
* The events recorded on the safety event report form must be consistent with the information entered on the AE CRFs.
* Include any relevant medical history, concurrent illnesses, and concomitant medicines.
* Include treatment(s) provided.
* The Investigator must assess causality at the time of the first SAE notification.
* The Investigator is responsible for obtaining and forwarding details of the outcome of the SAE, as well as any other details which may be requested by AnaptysBio and/or Quintiles in a timely manner:
  + Hospital records o Medical records o Data clarification
  + Death certificate/autopsy results
  + Events should be followed until they are resolved or stabilized, “Resolved with sequelae” will require specification of the sequelae.
  + For a fatal or life-threatening SAE, call Quintiles Safety Group (contact information is located on the SAE form), in addition to faxing the completed SAE form.
  + The SAEs should continue to be reported for at least 5.5 half-lives of study product following last dose.
  + Queries on SAE reports will be generated when there is missing/discrepant information, or when there is a need for additional information to completely evaluate the report. All supplemental SAE information and or documentation is to be submitted upon request.

#### 7.1.1.2 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

All SAEs that are considered unexpected and related to the IP will be reported by Quintiles as a 15-Day report to the regulatory authorities as applicable and to all participating Investigators. The SAEs that are considered unexpected, related to the study and are life-threatening or result in death will be reported by Quintiles to the regulatory authorities as applicable, and to all participating Investigators as a 7-Day report. Quintiles will ensure that all SAEs are reported to the appropriate regulatory authorities.

Investigators will be notified by Quintiles of all SAEs that require prompt submission to their Institutional Review Board (IRB). Each Investigator must notify the IRB/IEC responsible for reviewing the study at their site of all 15-Day or 7-Day safety reports required by local regulations or IRB/IEC requirements and should provide written documentation of IEC notification for each report to Quintiles. This study will comply with all local regulatory requirements and adhere to the full requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

#### 7.1.1.3 Follow-Up of Adverse Events

Any AEs observed from screening up to the end of the study will be followed up to resolution. Resolution means that the patient has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE or the patient is deemed lost to follow-up. All AEs that occur after the patient completed a clinical study should also be reported to AnaptysBio and/or Quintiles within 30 days of the patient’s last visit.

### 7.1.2 Clinical Laboratory Evaluations

Blood samples for hematology, clinical chemistry evaluations including serum pregnancy test and serological assays, will be collected at the visits specified in Table 4.1. A list of specific clinical laboratory evaluations is provided in Table 7.1 below:

##### Table 7.1 Clinical Laboratory Parameters

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Hematology** | **Clinical Chemistry** | **Virology** | **Urinalysis** | **Drugs of Abuse**  **(*Only at screening)*** |
| Hematocrit  Packed Cell Volume  Hemoglobin  Mean Cell  Haemoglobin  Mean Cell Hemoglobin  Concentration  Mean Cell Volume  Platelet Count  Red Blood Cell Count  White Blood Cell Count  Basophils  Eosinophils Monocytes  Neutrophils  Lymphocytes  Immunoglobulins | ALT  Albumin  ALP  AST  Bicarbonate  Bilirubin (Total)  Bilirubin (Direct) (only if  Total is elevated)  Calcium  Chloride  C-Reactive Protein  Creatinine  GGT  Glucose  Potassium  Phosphate (Inorganic)  Protein (Total) | Hepatitis B  Surface  Antigen  Hepatitis C  Antibody  HIV Antibody      **TB screening**  Quantiferon  Gold® test *(only done at*  *screening*  *visit)* | Bilirubin  Blood  Glucose  Ketones  Leukocytes Nitrates pH  Protein  Specific gravity  Urobilinogen    **At discretion of Investigator based on urinalysis results**  Microbiology | Amphetamines  Barbiturates  Benzodiazepines  Cocaine  Marijuana/Cannabis  Methadone  Methamphetamine/  Ecstasy  Morphine/Opiates  Phencyclidine  Tricyclic  Antidepressants |
| **Hematology** | **Clinical Chemistry** | **Virology** | **Urinalysis** | **Drugs of Abuse**  **(*Only at screening)*** |
| (IgA, IgG, IgM, IgE,  IgD) | Sodium  Troponin  Urea  **WOCBP Only** - hCG levels |  | Urine  Microscopy |  |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin hormone; HIV = human immunodeficiency virus; TB = tuberculosis; WOCBP = women of child bearing potential.

The central laboratory tests will be conducted by Quintiles Quest Joint Venturesituated at the following addresses:

The Alba Campus Rosebank Livingston West Lothian

EH54 7EG Scotland, United Kingdom

Phone: + 44 (0) 1506 81 4000

Fax: + 44 (0) 1506 814199

Quest House 125-135

Staines Road, Hounslow TW3 3JB, United Kingdom

Phone: + 44 (0) 208 377 3300

Fax: +44 208 377 3434

The clinical laboratory tests will be reviewed for results of potential clinical significance, based on Investigator’s discretion, at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

Blood samples (6 mL of whole blood) for ex vivo induced IFN-γ assessment on Days 1, 11, 64, 120, and 148 will be collected in a sodium heparin tube (See laboratory manual for detailed collection and processing instructions).

Serum samples (5 mL of whole blood) for ADA determination on Days 1, 11, 64, 120, and 148 will be collected using 5 mL Vacutainer® sST tube (See laboratory manual for detailed collection and processing instructions).

### 7.1.3 Vital Signs and Physical Findings

Vital signs will be measured and physical examinations and ECG will be performed at the time points indicated in Table 4.1.

Vital signs include pulse rate, respiratory rate, body temperature, systolic BP, and diastolic BP. The physical examination includes evaluation of general appearance, head, eyes, ears, nose, and throat, and pulmonary, cardiovascular, gastrointestinal, renal/genitourological, endocrine (including thyroid), musculoskeletal/spinal, lymphatic, and dermatologic systems.

A standard 12-lead ECG will be performed by a qualified physician or nurse. The following parameters will be documented: HR, PR interval, QRS interval, QT interval, and QTc interval. 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. See Section 6.2.3 for assessment of the AD.

### 7.1.4 Safety Monitoring

There is no data monitoring committee for this study.

Timely and complete reporting of safety information assists the Sponsor in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study patients; (2) a greater understanding of the overall safety profile of the IP; (3) recognition of dose-related investigational product toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

## 7.2 Pharmacodynamics

Samples (100 µL) of blister fluid will be obtained by aspirating the blister fluid using a 30-guage needle. The obtained blister fluid is then transferred to two 1.5 mL Eppendorf tubes for the determination of interstitial leukocytes and cytokines. The peripheral blood cells interstitial leukocytes and cytokines drawn from blisters at the site of the skin challenge will be measured to monitor for evidence of release and will include, but not be limited to IL-4, IL-5, IL-13, and IL-33. Differential WBC counts in blister fluid will be measured to monitor peripheral cell populations. Serum samples (5 mL of whole blood), on Day 5 and Day 12, will be taken in a serum separator tube until vacuum is exhausted and then centrifuged to obtain two (2) aliquots of serum transferred to polypropylene cryovials to measure circulating cytokines including, but not limited to IL-4, IL-5, IL-13, IL-33 and sST2 (See laboratory manual for detailed collection and processing instructions). The serum and blister fluid biomarker time points are presented in Section 19.0.

The actual date and time of the sample collection will be recorded in the patient’s eCRF. The details of blood sample collection, sample tube labelling, sample preparation, storage, and shipping procedures will be described in a separate laboratory manual.

The measurement of interstitial leukocytes and cytokines, peripheral blood cell counts, and circulating cytokines, and ex vivo induced IFN-γ will be performed using validated assay methods. The analytical methods used to measure these PD endpoints will be described in a separate bioanalytical report.

## 7.3 Pharmacokinetics

Samples (5 mL) of whole blood will be obtained in a 5 mL Vacutainer® sST tube for the determination of ANB020 in human serum. Samples will be collected according to the schedule presented in Section 19.0. Approximately 50 mL of whole blood will be obtained from each patient for PK assessments during the study.

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

The actual date and time of the blood sample collection will be recorded in the patient’s eCRF. The details of blood sample collection, sample tube labelling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

**Bioanalysis**

The measurement of the concentrations of ANB020 will be performed using a validated assay method. The analytical methods used to measure concentrations of ANB020 will be described in a separate bioanalytical report.

## 7.4 Efficacy

Refer to Section 6.2.3 for description of the variables collected related to AD.

Although this study is exploratory and not statistically powered, efficacy assessments will be analyzed to assist in designing future studies. Efficacy assessments include EASI, IGA, SCORAD, DLQI, and 5D Itch Score.

## 7.5 Health Outcomes

Not applicable.

## 7.6 Pharmacogenetics

Not applicable.

## 7.7 Appropriateness of Measurements

All safety assessments used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant.

# 8.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (GCP) (CPMP/ICH/135/95), Quintiles 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 Qualification visit
* Center Initiation visit
* 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, AnaptysBio and/or Quintiles Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study center, center visits, 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 AnaptysBio’s representatives and regulatory authorities.

## 8.1 Monitoring

AnaptysBio has engaged the services of a contract research organization, Quintiles, to perform all monitoring functions within this clinical study. Quintiles’ monitors will work in accordance with Quintiles SOPs and have the same rights and responsibilities as monitor from AnaptysBio.

The monitor will establish and maintain regular contact between the Investigator and AnaptysBio.

The monitor will evaluate the competence of the study center, informing AnaptysBio 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 patients 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 IP, ensure proper IP 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 patients 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%:

* Patient identification number
* Patient consent obtained
* Patient eligibility criteria (inclusion and exclusion criteria)
* Efficacy variables
* Safety variables
* Medical record of AE

## 8.2 Data Management/Coding

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

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 patients.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient’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 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 patient’s medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient’s participation in the study. They include but are not limited to laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

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 patient who receives IP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient 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.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

## 8.3 Quality Assurance Audit

Study centers, the study database and study documentation may be subjected to Quality

Assurance audit during the course of the study by AnaptysBio or Quintiles on behalf of

AnaptysBio. In addition, inspections may be conducted by regulatory bodies at their discretion.

# 9.0 STATISTICS

Statistical analyses will be performed by Quintiles using statistical analysis system (SAS®), (SAS Institute, Cary, NC, USA) Version 9.2 or higher. Quintiles’ SOPs and work instructions will be used as the default methodology if not otherwise specified.

Details of statistical analysis methods will be provided in the SAP that will be prepared and signed off prior to database lock. Any change to the data analysis methods will be mentioned in the Statistical Analysis Plan (SAP). Any additional analyses, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

## 9.1 Determination of Sample Size

As this is the first study of this type with an anti-IL-33 inhibitor, the number of patients to be enrolled is not based on statistical power considerations.

A total of 12 patients will be sequentially dosed with placebo followed by HDM and saline skin challenge. Patients who have had a positive response to the HDM skin challenge will receive a single dose of ANB020 followed approximately 24 hours later with an HDM and saline skin challenge test administration.

Patients who enroll and withdraw before receiving ANB020 will be replaced. Dropouts after receiving the dose of ANB020 will be replaced if they withdraw prior to returning to the study center for Day 12 (within 24 hours of the skin challenge) assessments.

## 9.2 Analysis populations

**Efficacy Analysis Set**

All patients who have received ANB020 and provide efficacy data on Day 15. The full analysis set will be used for all efficacy analyses.

**Safety Analysis Set**

All patients who have received at least one dose of ANB020. The safety analysis set will be used for all safety analyses.

**Pharmacokinetics Analysis Set**

All patients who have at least one post-dose serum concentration data value available for ANB020. The PK analysis set will be used for all PK analyses.

**Pharmacodynamics Analysis Set**

All patients who have received at least one dose of ANB020 or placebo and provide an evaluable post-dose PD measurement. The PD analysis set will be used for all PD analyses.

## 9.3 Patient Disposition

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, enrolled, not positive response to the HDM skin challenge, assigned treatment ANB020, completed till Day 12, completed as well as the number of dropouts, with reasons for discontinuation and major protocol deviations or violations. A listing will be presented to describe dates of screening, assigned treatment, screen failed with reason, completion or early withdrawal and the reason for early discontinuation, if applicable, for each patient. A list of protocol violations will be identified and discussed with the Investigator/AnaptysBio in dry-run to categorize as major or minor and the same will be reported.

## 9.4 Patient Characteristics and Concomitant Medications

Patient characteristics will be obtained at screening will be summarized for all patients taking

ANB020 and placebo. Summaries will include descriptive statistics for continuous variables (sample size [n], mean, standard deviation [SD], median, minimum, and maximum) and for categorical variables (sample size, frequency, and percent). Patient characteristics may include, but are not limited to age, gender, race/ethnicity, height, weight, and BMI.

Categorical use of concomitant medication will be summarized by treatment period and overall. All concomitant medications used will be listed.

## 9.5 Efficacy Analyses

Following are the secondary efficacy endpoints:

* Urticarial manifestations 0.5 hours after HDM challenge at site of challenge.
* Clinical scores such as EASI, IGA, SCORAD, DLQI, and 5D Itch Score.
* Patient diary data of corticosteroid usage.

For the quantitative efficacy variables, descriptive statistics (including n, mean, minimum, maximum, and 95% CI) will be presented. Corticosteroid usage and urticarious will be summarized with number and percentage of patients. Clinical scores over a period of 8 weeks after and Day 64 to Day 148 after administration of the IP will be using a Mixed-Model

Repeated Measures analysis. Further details of efficacy analysis will be specified in the SAP.

## 9.6 Safety Analyses

Following are the safety and tolerability endpoints:

* Assessment of AEs
* Potential significance and clinical importance AEs, SAEs, AESIs, and AEs leading to withdrawal
* Physical examinations
* Vital signs
* Clinical safety laboratory tests (hematology, biochemistry, and urinalysis)
* Assessment of ex vivo PD activity on IFN-γ levels
* Assessment of immunogenicity (ADA levels)
* Electrocardiogram

### 9.6.1 Adverse Events

Adverse events will be coded using the MedDRA. For each study treatment period, numbers of events and percentage will be tabulated by preferred term and system organ class. An event that occurred one or more times on treatment period will contribute one observation to the numerator and denominator comprise all safety patients exposed to ANB020. 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, AEs leading to treatment discontinuation and AEs leading to withdrawal of patient will be tabulated for each treatment period.

Summaries over SOC, PT and listings of AEs, AEs leading to death, SAEs, potentially significant AEs, clinically important AEs, and AEs that led to discontinuation from the study or of the IP will be presented by treatment period (placebo dosing and then active ANB020 dosing periods). Summaries will also be presented by relatedness to the IP and the severity of the AE.

### 9.6.2 Vital Signs Measurements, Physical Findings and Clinical Laboratory

#### Evaluations

Summaries and listings of data for vital signs, hematology, clinical chemistry and urinalysis laboratory tests, ECGs and physical examination findings 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 clinical chemistry tests, listings of patient 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.

For ECG variables, the QT correction factor will be based on both the Bazett and Fridericia formulae (QTcB and QTcF). Categorical summaries of absolute QT, QTcB and QTcF values and change from (baseline) values in QT, QTcB and QTcF values will be presented by treatment and visit.

Descriptive statistics will be used to present the safety outcomes including, physical examination results, weight, BMI, vital signs measurements, clinical laboratory test results, and ECG results. Change from baseline will also summarized for vital signs measurements, clinical laboratory test results.

Observed ex vivo induced IFN-γ levels and ADA levels will be summarized with descriptive statistics. Means will compared between ANB020 and placebo using mixed-effect Analysis of Covariance (ANCOVA). Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI. Log transformations will be applied as appropriate. Graphical summaries will be generated, as appropriate.

The relationship between ANB020 concentrations and ex vivo induced IFN-γ levels, ADA levels will be explored graphically and statistically.

### 9.6.3 Missing Data

No imputation will be performed for the missing data.

### 9.6.4 Pharmacokinetic Analyses

### 9.6.5 Evaluation of Pharmacokinetic Data

The PK parameters will be derived using non-compartmental methods. The actual sampling times will be used in the PK parameter calculations. The PK analyses will follow Quintiles SOPs. Further details of PK analysis will be specified in the SAP.

Where possible, the following PK parameters will be determined for ANB020 after a single IV infusion:

* Maximum observed concentration (Cmax)
* Time to maximum observed concentration (tmax)

Additional PK parameters may be determined if deemed appropriate.

### 9.6.6 Pharmacokinetic Concentration Data Analyses

A patient listing of all concentration-time data for each treatment will be presented.

Concentration data of ANB020 will be summarized by treatment and nominal time point using the number of observations (n) and number of observations ≥lower limit of quantification (LLOQ), arithmetic mean, SD, coefficient of variation (CV), minimum, median, and maximum.

Graphs of concentration-time data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

### 9.6.7 Pharmacokinetic Parameter Data Analyses

All PK parameters will be summarized by treatment using n, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean (Gmean), and geometric CV (gCV) defined as



where ‘s’ is the SD of the data on a log scale, except that tmax will be reported with n, minimum, median, and maximum only.

Graphs of parameters may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

## 9.7 Pharmacodynamic Analyses

The primary PD endpoints are observed cytokines from interstitial fluid sampling, and change in differential WBC. The exploratory PD endpoint will be change in leukocytes from interstitial fluid sampling.

Observed interstitial leukocytes, cytokines and WBC differentials will be summarized with descriptive statistics. Means will compared between ANB020 and placebo using mixed-effect analysis of covariance (ANCOVA). Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI. Log transformations will be applied as appropriate. Graphical summaries will be generated, as appropriate.

Observed and change from baseline for serum cytokines will be summarized with descriptive statistics. Change from baseline for serum cytokines will be compared between ANB020 and placebo using mixed-effect ANCOVA. Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI. Graphical summaries will be generated, as appropriate.

The relationship between ANB020 concentrations and PD endpoints will be explored graphically and statistically.

## 9.8 Interim Analyses

No interim analysis is planned for this study.

# 10.0 ETHICS

## 10.1 Independent Ethics Committee

An Independent Ethics Committee (IEC) should approve the final protocol, including the final version of the Informed Consent Form (ICF) and any other written information and/or materials to be provided to the patients. The Investigator will provide AnaptysBio or Quintiles with documentation of IEC approval of the protocol and informed consent before the study may begin at the study center. The Investigator should submit the written approval to AnaptysBio or representative before enrolment of any patient into the study.

AnaptysBio or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to AnaptysBio or Quintiles of required IEC’s annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IEC, any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IEC as per IEC’s requirements. Upon completion of the study, the Investigator will provide the IEC with a brief report of the outcome of the study, if required.

The ERA Consulting (UK) Ltd. or representative will handle the distribution of any of these documents to the national regulatory authorities.

Quintiles or a representative will provide Regulatory Authorities, IEC, and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

Each Investigator is responsible for providing the IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. Quintiles or a representative will provide this information to the Investigator so that he/she can meet these reporting requirements.

## 10.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2008), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

## 10.3 Patient Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of IP. The Investigator will provide each patient with a copy of the signed and dated ICF.

## 10.4 Patient Data Protection

Not applicable, as pharmacogenetic evaluations will not be conducted for this study.

# 11.0 STUDY ADMINISTRATION

## 11.1 ADMINISTRATIVE STRUCTURE

##### Table 11.1 Administrative Structure

|  |  |
| --- | --- |
| **Sponsor**  AnaptysBio Inc.  10421 Pacific Center Ct Suite 200  San Diego, CA 92121  United States | **Drug Safety Monitoring**  Quintiles  Customer Safety Services  Global Data & Safety Monitoring 5927 S. Miami Blvd.  Morrisville, NC 27560  United States |
| **Clinical Study Supply Management**  IP:  AnaptysBio Inc.  10421 Pacific Center Ct Suite 200  San Diego, CA 92121  United States    Ancillary supplies:  Quintiles  10188 Telesis Court, Suite 400  San Diego, CA 92121  United States | **Data Management**  Quintiles  Data Management  Etamin Block (Building B3)  Prestige Technology Park II  Sarjapur-Marathalli Outer Ring Road  Bangalore - 560103  India |
| **Clinical Laboratory**  Q2 Solutions  Multiple locations | **Biostatistics**  Quintiles  Biostatistics  12th Floor, G-Corp Tech Park, Near Hypercity Mall,  Ghodbunder Road, Kasarwadawli, Thane (West),  Thane - 400 607  India |
| **Study Monitoring**  Quintiles  10188 Telesis Court, Suite 400  San Diego, CA 92121  United States | **Medical Writing**  Quintiles  Global Medical Writing and Document Publishing  12th Floor, G-Corp Tech Park  Ghodbunder Road, Kasarwadawli, Thane (West)  Thane - 400 607  India |
| **Medical Monitoring** AnaptysBio Inc.  10421 Pacific Center Court, Suite 200  San Diego, CA 92121  United States |  |

## 11.2 Data Handling and Record Keeping

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 International Council for Harmonisation (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 IP. 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. Patient identification codes (patient 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 AnaptysBio, who agrees to abide by the retention policies. Written notification of transfer must be submitted to AnaptysBio. The Investigator must contact AnaptysBio prior to disposing of any study records.

## 11.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient randomized into the study.

The Investigator will allow AnaptysBio, Quintiles, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual patient medical records, as appropriate. Such information must be kept confidential and must have locked facilities that allow for this. Patient identification number and not the patient’s name will be recorded on all documents related to the study.

## 11.4 Investigator Information

### 11.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997), European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator is responsible for ensuring that all study center personnel, including subInvestigators, adhere to all applicable regulations and guidelines, including local laws and regulations, regarding the study both during and after study completion. The Investigator is responsible for informing the IEC of the progress of the study and for obtaining annual IEC renewal. The Investigator is responsible for informing the IEC of completion of the study and will provide the IEC with a summary of the results of the study.

### 11.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to AnaptysBio or the representative (Section 18.0). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

### 11.4.3 Publication Policy

The data generated by this study are confidential information of AnaptysBio. AnaptysBio 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.

## 11.5 Financing and Insurance

AnaptysBio will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

# 12.0 REFERENCES

1. Pastorelli L., Garg RR, Hoang SB., Spina L, Mattioli B., Scarpa M., et al. Epithelial-derived IL-33 and its receptor ST2 are dysregulated in ulcerative colitis and in experimental Th1/Th2 driven enteritis. Proc. Natl. Acad. of Sci USA. 2010 Apr 27;107(17):8017-8022.
2. Liew Fy. Il-33: A Janus Cytokine. Ann Rheum Dis. 2012 Apr; 71(Suppl 2):I101-I104.
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4. Montes-Torres A, Llamas-Velasco M, Pérez-Plaza A, Solano-López G and Sánchez-Pérez J.

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2. Crack LR, Chan HW, McPherson T, and Ogg GS. Identification of an immunodominant region of the major house dust mite allergen Der p 2 presented by common human leucocyte antigen alleles. Clin. Exp. Dermatol. 2012 Apr;37(3):266-276.
3. Guidance for industry. Exposure-Response relationships-Study Design, Data Analysis, and Regulatory Applications. U.S. Department of Health and Human Services Food and Drug Administration Guidance Document 2003 Apr; Section III A.page 3.
4. EASI Scoring System. Available from:

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Protocol Number: ANB020-002 ANB020

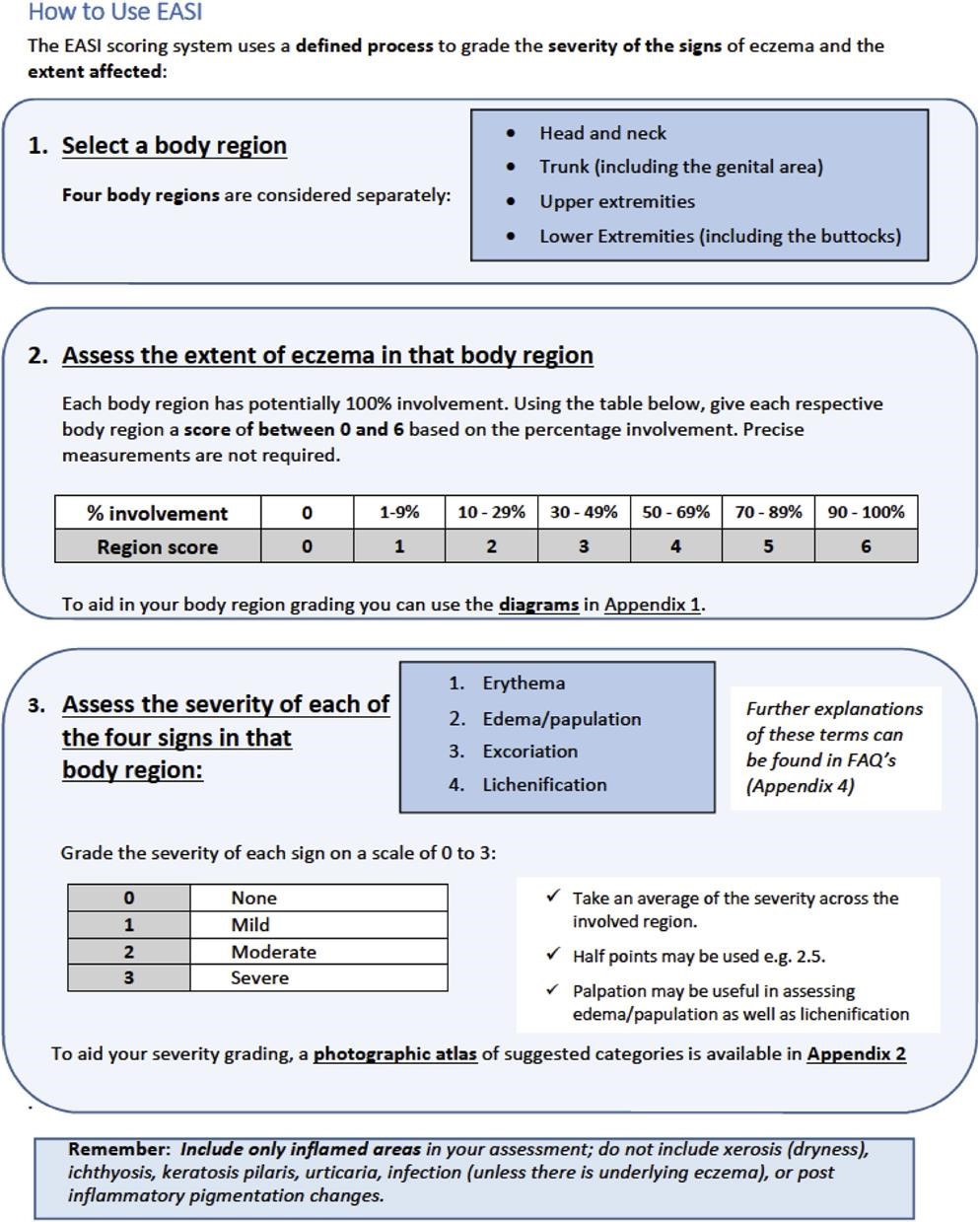
# 13.0 APPENDIX I

**Hanifin and Rajka guidelines for the diagnosis of AD**.

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, 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, 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, delayed blanch

# 14.0 APPENDIX II

**EASI score for the diagnosis of AD:**



**How to record an EASI score:**

**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** |

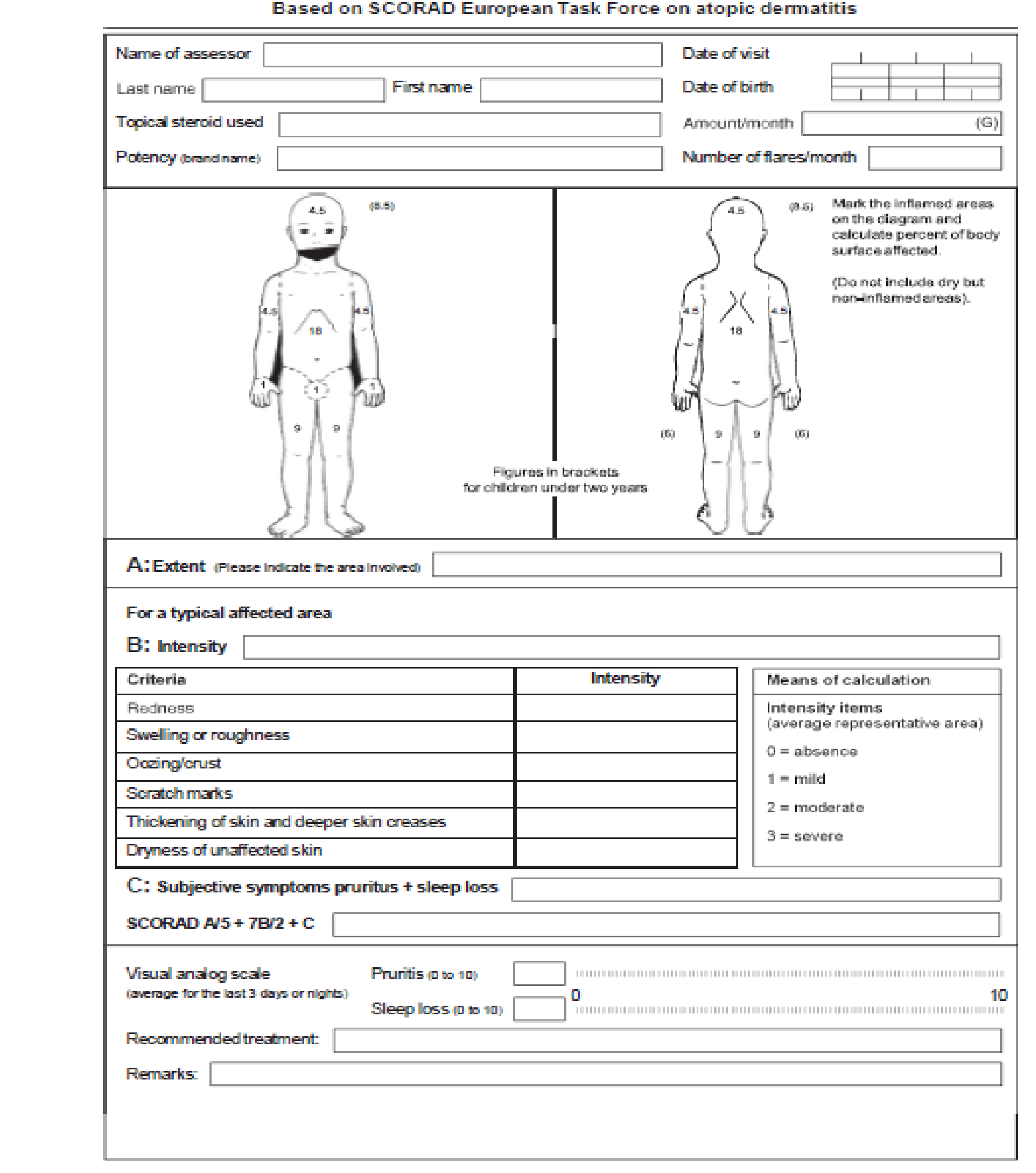
* Take an average of the severity across the involved area.
* Half points may be used e.g. 2.5.

**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)** |

# 15.0 APPENDIX III

**SCORAD index for the diagnosis of AD:**



**How to record a SCORAD score:**

**Area:**

To determine extent, the sites affected by eczema are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body.

* Head and neck 9%
* Upper limbs 9% each
* Lower limbs 18% each
* Anterior trunk 18%
* Back 18%
* 1% for genitals.

The score for each area is added up. The total area is 'A', which has a possible maximum of 100%.

**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 i.e., itch and sleeplessness, are each scored by the patient 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.

# 16.0 APPENDIX IV

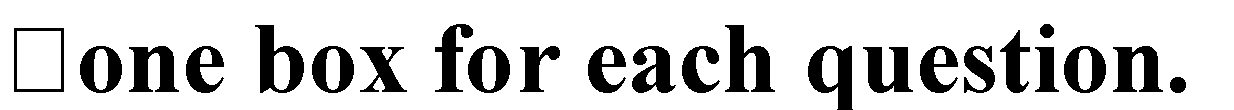
**DLQI Scale for the diagnosis of AD:**

**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** 



1. Over the last week, how **itchy**, **sore**, Very much **painful** or **stinging** has your skin A lot been? A little



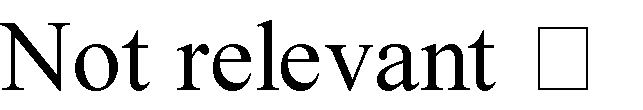
Not at all

1. Over the last week, how **embarrassed** Very much or **self conscious** have you been because A lot of your skin? A little



Not at all

1. Over the last week, how much has your Very much skin interfered with you going A lot **shopping** or looking after your **home** or A little

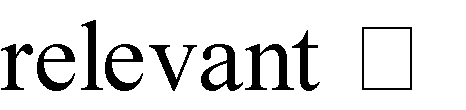


**garden**? Not at all

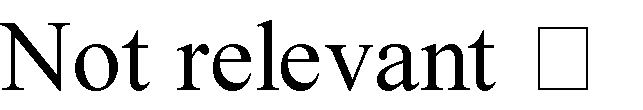
1. Over the last week, how much has your Very much skin influenced the **clothes** A lot you wear? A little



Not at all Not

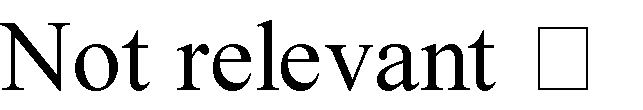


1. Over the last week, how much has your Very much skin affected any **social** or A lot **leisure** activities? A little



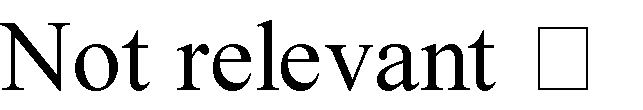
Not at all

1. Over the last week, how much has your Very much skin made it difficult for A lot you to do any **sport**? A little



Not at all

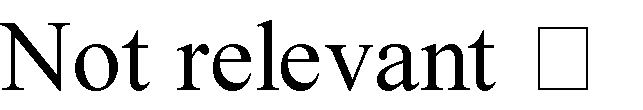
1. Over the last week, has your skin prevented Yes you from **working** or **studying**? No



If "No", over the last week how much has A lot your skin been a problem at A little

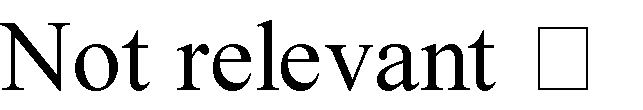
**work** or **studying**? Not at all

1. Over the last week, how much has your Very much skin created problems with your A lot **partner** or any of your **close friends** A little



or **relatives**? Not at all

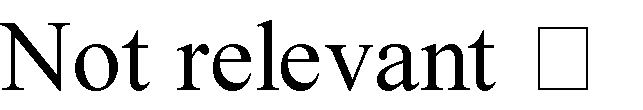
1. Over the last week, how much has your Very much



skin caused any **sexual** A lot **difficulties**? A little

Not at all

1. Over the last week, how much of a Very much problem has the **treatment** for your A lot skin been, for example by making A little your home messy, or by taking up time? Not at all



**Please check you have answered EVERY question. Thank you.**

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# 17.0 APPENDIX V

**5D Itch Scale for the diagnosis of AD:**

1. **Duration**: During the last 2 weeks, how many hours a day you have been itching?

Less than 6-12 12-18 18-23 All day

6hrs/day hrs/day hrs/day hrs/day

* 1. 2 3 4 5

1. **Degree:** Please rate the intensity of your itching over the past 2 weeks

Not Mild Moderate Severe Unbearable present

* 1. 2 3 4 5

1. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely Much Little bit Unchanged Getting resolved better better, worse

but still but still

present present

* 1. 2 3 4 5

1. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks.

Never Occasionally Frequently Delays Delays affects delays delays falling falling sleep falling falling asleep and asleep asleep asleep occasionally and

**Sleep** wakes me frequently

up at night wakes me

up at night

* 1. 2 3 4 5

**Leisure** N/A Never Occasionally Frequently Always

**/Social** affects this affects this affects this affects activity activity activity this

activity

1

2

3

4

5

1

2

3

4

5

**Housework**  **/Errands Work/School**  1 2 3 4 5

1. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

Present Present

Head/Scalp Soles

Face Palms

Chest Tops of

Hands/Fingers

Abdomen Forearms

Back Upper Arms

Buttocks Points of Contact

w/Clothing (e.g.

waistband

Thighs

Lower legs

Tops of Feet/Toes

©Br J Dermatol. 2010 March; 162(3): 587–593. doi:10.1111/j.1365-2133.2009.09586.x

# 18.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR

**PROTOCOL TITLE:** Placebo-Controlled Proof of Concept Study to Investigate ANB020

Activity upon House Dust Mite Skin Challenge in Patients Suffering from Moderate to Severe Atopic Dermatitis

**PROTOCOL NO:** ANB020-002

This protocol is a confidential communication of AnaptysBio. 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 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 AnaptysBio.

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

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: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Protocol Number: ANB020-002

ANB020

# 19.0 APPENDIX 2: PHARMACOKINETIC/SERUM AND BLISTER FLUID BIOMARKER

## TIME POINTS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study Visit** | **PK Sample Time Point (Serum)** | **PD Sample Time Point for Cytokines (Blister Fluid)** | **PD Sample Time Point for Cytokines (Serum)** | **Sample Time Point for ex vivo induced IFN-γ Samples** | **Sample Time Point for**  **ADA** |
| Day 1 |  |  | Pre-Dose (-30 minutes) | Pre-Dose (-30 minutes) | Pre-Dose (-30 minutes) |
|  |  |  |  |  |  |
| Day 5 |  | 24 hours (±1 hour) postHDM Skin Challenge [96 hours (±8 hours) post-start of infusion w/Pbo] | 24 hours (±1 hour) postHDM Skin Challenge [96 hours (±8 hours) post-start of infusion w/Pbo] |  |  |
|  |  |  |  |  |  |
| Day 8  ANB020  Dosing | Pre-Dose (-30 minutes) |  | Pre-Dose (-30 minutes) |  |  |
| 0.50 hours (±5 min) post-start of infusion w/ANB020 |  |  |  |  |
| EOI (+≤ 3 min) |  |  |  |  |
| EOI+3 hours (±10 min) |  |  |  |  |
| EOI+6 hours (±10 min) |  |  |  |  |
|  |  |  |  |  |  |
| Day 11 on study | 72 hours (±4 hours) post-start of infusion w/ANB020 |  |  | 72 hours (±4 hours) post-start of infusion w/ANB020 | 72 hours (±4 hours) post-start of infusion w/ANB020 |
|  |  |  |  |  |  |
| Day 12 on study | 96 hours (±8 hours) post-dose w/ANB020 | 24 hours (±1 hour) postHDM Skin Challenge [96 hours (±8 hours) post-start of infusion w/ANB020] | 24 hours (±1 hour) postHDM Skin Challenge [96 hours (±8 hours) post-start of infusion w/ANB020] |  |  |
|  |  |  |  |  |  |
| Day 64 | 1344 hours (±48 hours) post-start of infusion w/ANB020 |  |  | 1344 hours (±48 hours) post-start of infusion w/ANB020 | 1344 hours (±48 hours) post-start of infusion w/ANB020 |

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study Visit** | **PK Sample Time Point (Serum)** | **PD Sample Time Point for Cytokines (Blister Fluid)** | **PD Sample Time Point for Cytokines (Serum)** | **Sample Time Point for ex vivo induced IFN-γ Samples** | **Sample Time Point for**  **ADA** |
|  |  |  |  |  |  |
| Day 120 | 2688 hours (±120 hours) post-start of infusion w/ANB020 |  |  | 2688 hours (±120 hours) post-start of infusion w/ANB020 | 2688 hours (±120 hours) post-start of infusion w/ANB020 |
|  |  |  |  |  |  |
| End of  Study  Day 148 or  ET | 3360 hours (±120 hours) post-start of infusion w/ANB020 |  |  | 3360 hours (±120 hours) post-start of infusion w/ANB020 | 3360 hours (±120 hours) post-start of infusion w/ANB020 |

Abbreviations: ADA = Anti-drug Antibody, EOI = actual time of end of infusion; ET = End of Treatment; HDM = house dust mite; min = minutes; IFN-γ = Interferon-Gamma, Pbo = Placebo; PD = pharmacodynamic; PK = pharmacokinetic

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Protocol Number: ANB020-002 ANB020

# 20.0 APPENDIX 3: SUMMARY OF CHANGES

**Protocol ANB020-002: Amendment 2.0, 01 December 2016**

**Replaces: Amendment 1.0, 08 November 2016**

1. List of abbreviations

Description of Change: Added HIV.

Purpose for Change: To reflect the addition in exclusion criteria and abbreviations used

1. Section 4.3.2

Description of Change: Added text regarding a patient will not be enrolled in the study if they have a positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV 1 and 2 antibodies at screening.

Purpose for Change: To ensure safety of potential patients to be enrolled.

**Protocol ANB020-002: Amendment 1.0, 08 November 2016**

**Replaces: Original: 14 September 2016**

1. Throughout the document

Description of Change: Significant changes in protocol design, safety (assessments) and duration of the study.

Purpose for Change: Clarity requested by MHRA during their review.

1. Synopsis

Description of Change:

* + 1. Study Duration approx. 23 weeks, (162 days), Treatment and Follow-up =148 days.
    2. ANB020 on severe to moderate AD will be monitored over a period of 20 weeks.
    3. Additional text added for Day 85, 120, and EOS (Day 148).
    4. Added text regarding ADA, and IFN-γ samples to be obtained at Day 1 Pre-dose,

Day 11 post-dose, Day 64, Day 120, and Day 148 (EOS)

* + 1. Under Primary Safety and Tolerability Endpoints;

i. Measure ANB020 Ex-vivo inhibition cytokine release (IFN-γ) ii. Immunogenicity to ANB020 Anti-drug Antibody (ADA)

Purpose for Change: To ensure safety assessments and duration of study is captured.

1. List of abbreviations

Description of Change: Added ADA and IFN-γ.

Purpose for Change: To reflect the changes in safety assessments and abbreviations used.

1. Section 3.2

Description of Change:

* 1. Added to objectives assess the ex vivo PD activity of ANB020 on IFN-γ levels.
  2. Added to objectives test for any immunogenicity to ANB020 Purpose for Change: To reflect the changes in study conduct.

1. Section 4.1

Description of Change: Added text regarding additional days (85, 99, 120, 148 [EOS]) PK draws and PD/ADA and Clinical Assessments

Purpose for Change: To reflect the changes in study conduct.

1. Figure 1

Description of Change: Updated to reflect new Schedule of Events.

Purpose for Change: To reflect the changes in protocol design.

1. Table 4.1 (Schedule of Events [SOE]) Description of Change:
   1. Updated SOE to show additional study center visits at: Day 85, Day 120, and Day 148 [EOS]).
   2. Added additional Telephone contact visit at Day 99
   3. Added to SOE:
      * + 1. Additional PK draws on Day 120 and 148,
          2. Added whole blood sampling for ex vivo IFN-γ to (Day 1, 11, 64, 120 and 148) iii. Added Serum Sampling for ADA (Day 1, 11, 64, 120 and 148)
        1. Added AESI, IGA, SCORAD, DLQI, 5Ditch, Corticosteroid use to be obtained on Day 85, 120, 148
        2. Added urinalysis and safety laboratory assessments to Day 85, 120 and 148 (EOS)
        3. Moved PE and pregnancy test (WOCBP) to be Day 148 (EOS) from Day 64 vii. Added Diary to be checked at Day 85, 99, 120 and 148 (EOS)

viii. Added concomitant medications/AEs to each new time point

* 1. Added any additional Foot notes as necessary to account for ADA, IFN-γ, and additional days

Purpose for Change: To reflect the changes in study conduct.

1. Section 4.2

Description of Change: Modified text to be “Following patients for approximately 4.6 months after ANB020 administration will allow time for PK, PD, and safety assessments from a single dose.”

Purpose for Change: To reflect the changes in study conduct.

1. Section 4.3.1 and Section 4.3.4

Description of Change: Modified text to describe methods and duration of contraception for WOCB and Male patients

Purpose for Change: To provide clarity and ensure all patients are using highly effective methods of contraception throughout the study.

1. Section 4.3.5

Description of Change: Revised text to account for EOS to be Day 148 for AEs/SAE follow-up.

Purpose for Change: To reflect the changes in study conduct.

1. Section 5.7

Description of Change: Revised text to accurately reflect the study is not blinded.

Purpose for Change: To reflect the changes in study conduct.

1. Section 5.8.1

Description of Change: Added additional Bullet: Any live attenuated vaccine within 4 weeks of screening and for the duration of the study (Day 148) or for 140 days post last dose of IP.

Purpose for Change: To reflect the changes in study conduct.

1. Section 6.2.1 (Table 6.1)

Description of Change: Revised total blood volume, to Visits/Days and blood volumes based upon revised Schedule of Events (Table 4.1).

Purpose for Change: To reflect the changes in study conduct.

1. Section 7.2

Description of Change:

* 1. Added text regarding obtaining the (6 mL of whole blood) for ex-vivo IFN-γ samples on Days 1, 11, 64, 120 and 148 will be collected in a Sodium Heparin Tube and process per laboratory processing manual.
  2. Added text for ADA sample using 5 mL Vacutainer SST tube for determination of anti-drug antibodies.

Purpose for Change: To reflect the changes in study conduct.

1. Section 9.6

Description of Change: Added bullets for ex-vivo PD activity on IFN-γ levels and assessment of immunogenicity (ADA levels).

Purpose for Change: To reflect the changes in study conduct.

1. Section 9.6.2

Description of Change: Added text regarding statistical analysis to be performed with IFN-γ and ADA data.

Purpose for Change: To reflect the changes in study conduct.

1. Section 19.0 (Appendix 2.0)

Description of Change: Following was added:

* 1. ADA and ex vivo IFN-γ Samples Day 1 (pre-dose), Day 11, Day 64, Day 120, and Day 148.
  2. Added additional PK draws on Day 120 and Day 148.

Purpose for Change: To reflect the changes in study conduct.