Clinical Study Protocol

Protocol Title:	**Placebo-Controlled Proof of Concept Study to Investigate ANB020 Activity in Adult Patients with Severe Eosinophilic Asthma**
Protocol Number:	**ANB020-004**
Version:	**Amendment 3**
Date of Protocol:	**16 Feb 2018**
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EudraCT No.:	**2017-000647-40**
Study Phase	**IIa**
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Signatures

PROTOCOL TITLE: **Placebo-Controlled Proof of Concept Study to Investigate ANB020 Activity in Adult Patients with Severe Eosinophilic Asthma**

PROTOCOL NO: **ANB020-004**

[redacted] [redacted] 16th Feb 2018

Signature **Date**

AnaptysBio Inc.

[redacted] [redacted] 28/2/18

Signature **Date**

Chief Investigator

Oxford University Hospital and Trust

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 in Adult Patients with Severe Eosinophilic Asthma	
Protocol No:	ANB020-004	
Study centers:	Up to 6 centers in the United Kingdom	
Study duration: The expected duration of the study is up to 141 days. Screening period of 7-14 days and treatment and follow-up period of 127 days.		**Phase:** IIa

Objectives:

Primary:

- To measure the reduction of eosinophils (blood eosinophil count) from Baseline (Day 1 pre-dose) to Day 22 in adult severe eosinophilic asthma patients administered with ANB020.
- To assess the safety and tolerability of a single, intravenous (IV) dose of ANB020 compared to placebo in adult patients with severe eosinophilic asthma.

Secondary:

- To measure the reduction of eosinophils (blood eosinophil count) from Baseline (Day 1 pre-dose) to the End of Study (EOS) visit (Day 127) in adult severe eosinophilic asthma patients administered with ANB020.
- To assess the change from Baseline in the clinic forced expiratory volume in 1 second (FEV_1) from Baseline (Day 1 pre-dose) to the EOS visit (Day 127).
- To assess the change from Baseline in the fractional exhaled nitric oxide (FeNO) in the breath from Baseline (Day 1 pre-dose) to the EOS visit (Day 127).
- To assess the pharmacodynamic (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, IV dose in adult patients with severe eosinophilic asthma.

Exploratory:

- To assess the effect of ANB020 on circulating serum cytokines.
- To assess the activity of ANB020 after a single, IV dose on clinical scores such as the Asthma Control Questionnaire (ACQ), Patient Global Impression of Change (PGIC), and the Clinical Global Impression of Change (CGIC).
- To assess the effect of ANB020 on asthma symptoms, change in standard of care (SOC) treatment, and rescue medication (short-acting beta-agonists [SABA]) usage.
- To assess the effect of ANB020 on IgE levels.

Methodology:

This is a proof of concept study designed to assess the effects of a single 300 mg/100 mL IV dose of ANB020 compared to placebo in adult patients with severe eosinophilic asthma. This study will also assess the safety and tolerability of ANB020 in adult patients with severe eosinophilic asthma.

A written informed consent will be obtained from each patient prior to any study procedures. At the Screening visit (7-14 days before Day 1), inclusion and exclusion criteria will be assessed. Medical history, ongoing medications, as well as vital signs will be recorded. Various other study assessments including a physical examination, FeNO measurement, spirometry to determine FEV_1, and laboratory tests will be performed.

On Day 1, patients will present to the study center, and the inclusion and exclusion criteria will be verified. Eligible patients will be randomized to receive one IV dose of either ANB020 (300 mg/100 mL) or placebo (0.9% sodium chloride [100 mL]) in a 1:1 ratio. Specific study assessments and safety laboratory tests will be performed. Blood samples to determine the eosinophil count, ex vivo induced IFN-γ levels, anti-drug antibodies (ADA), serum cytokines, and serial samples for PK analysis will be collected. Patients will remain in the study center for approximately 6 to 8 hours to complete the study assessments. 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.

After completing the Day 1 assessments, all patients will be followed up for 18 weeks. During the follow-up period, patients will return to the study center for study assessments on Day 2, 8, 22, 36, 64, 85, and 106 and will be contacted via telephone by study staff on Day 50 and 57. The EOS visit will be on Day 127 (Week 18) at the study center.

All patients will undergo the FeNO and FEV_1 (spirometry) tests at each study center visit. An ACQ will be completed by all patients at each study center visit (except Day 2) and the patient diary must be completed on a daily and weekly basis. The Investigator will rate the patient's response using the CGIC scale and the patients will be asked to rate the degree of change in the overall asthma status using the PGIC scale (part of the diary card). During the follow-up period, other assessments including vital signs, safety laboratory testing, eosinophil count, PK, and biomarker analysis will be performed at specified time points.

Planned number of patients:	Approximately 24
Diagnosis and main criteria for inclusion:	Male or female patients (women of childbearing potential must be taking highly effective contraceptive measures) aged ≥18 to ≤65 years with a confirmed clinical diagnosis of eosinophilic asthma with documented blood eosinophil count ≥300 cells/μL despite receiving SOC treatment.
Test product, dose and mode of administration:	ANB020 is a humanized immunoglobulin subtype G1/kappa (IgG1/kappa) monoclonal antibody that specifically neutralizes the biological effects of human interleukin-33 (hIL-33). A single dose of 300 mg ANB020 will be administered on Day 1 over 1 hour by IV infusion in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with 0.9% sodium chloride.
Placebo, dose, and mode of administration:	A total dose of 100 mL of placebo (0.9% sodium chloride) will be administered on Day 1 over 1 hour by IV infusion.

Criteria for evaluation:

Primary Endpoints:

Primary Pharmacodynamic Endpoint:

- Reduction of peripheral eosinophil count from Baseline (Day 1) to Day 22.

Safety and Tolerability Endpoints:

- Assessment of AEs/SAEs (potentially significant and clinically important AEs, SAEs, and AEs

leading to withdrawal).

- Physical examinations.
- Vital signs.
- Clinical safety laboratory tests (hematology, biochemistry, immunoglobulins, and urinalysis).
- Electrocardiogram (ECG).
- Number of asthma exacerbations.
- Immunogenicity to ANB020 ADA.

Secondary Endpoints:

Secondary Pharmacodynamic Endpoint:

- Reduction of peripheral eosinophil count from Baseline (Day 1) through EOS visit (Day 127).
- Whole blood ex vivo induced IFN-γ levels.

Secondary Efficacy Endpoints:

- Change in FEV_1 from Baseline (Day 1) to the EOS visit (Day 127).
- Change in FeNO from Baseline (Day 1) to the EOS visit (Day 127).

Secondary Pharmacokinetic Endpoints:

Where possible, the following limited PK parameters will be determined.

- Maximum observed concentration (C_{max}).
- Time to maximum observed concentration (t_{max}).

Exploratory Endpoints:

- Circulating cytokines including, but not limited to IL-4, IL-5, IL-9, IL-13, IL-33, and sST2.
- Clinical scores for ACQ, PGIC, and CGIC.
- Patient diary data of asthma symptoms, change in SOC treatment, and rescue medication (SABA) usage.
- Reduction of IgE levels from Baseline (Day 1) to the EOS visit (Day 127).

Statistical methods:

A total of approximately 24 patients will be randomized in a 1:1 ratio to receive ANB020 or placebo.

For primary PD endpoint, peripheral eosinophil count on Day 22 will be analyzed by a mixed-model repeated measures (MMRM) analysis with terms for treatment, time point of measurement, and treatment by time point interaction as fixed effects and Baseline eosinophil count (pre-dose measurement at randomization [Day 1]) as covariate. Appropriate correlation matrix will be used. Treatment differences will be presented with corresponding p-values for the test of no difference and 95% confidence interval (CI). Observed and change from Baseline will be summarized descriptively by nominal time point and treatment.

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 investigational product (IP) discontinuation will be summarized using the current MedDRA dictionary. Similar analyses will be performed for potentially significant and clinically important AEs. Number of asthma exacerbations will be summarized using frequency count and percentage. Observed and change from Baseline for ADA levels will be summarized with descriptive statistics.

Summaries and listings of vital signs, physical examination, ECG, and laboratory test results 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 IP

administration.

For secondary efficacy endpoint, actual and change in FEV_1 from Baseline (Day 1) to the EOS visit (Day 127) will be summarized using descriptive statistics. Change from Baseline will be compared between ANB020 and placebo using a mixed-effect analysis of covariance (ANCOVA). Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI.

As a supportive analysis, MMRM analysis will be used to assess the treatment effects. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 or with 2-sided 95% CIs. Other secondary efficacy endpoint and applicable exploratory endpoints analyses will be performed same as FEV_1 analyses.

For the quantitative efficacy variables, descriptive statistics (sample size, mean, minimum, maximum, and 95% CI) will be presented.

ANB020 concentrations in serum will be listed and summarized using appropriate descriptive statistics.

For secondary and exploratory PD endpoints, observed and change from Baseline for ex vivo induced IFN-γ, eosinophil count, and serum cytokines will be summarized descriptively by nominal time point and treatment. Comparison between ANB020 and placebo will be performed using a similar MMRM analysis as described for primary PD endpoint. The relationship between ANB020 concentrations and PD endpoints will be explored graphically.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body mass index
BP	Blood pressure
CGIC	Clinical Global Impression of Change
CI	Confidence interval
C_{max}	Maximum observed concentration
CV	Coefficient of variation
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of Study
ET	Early Termination
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma Assessment
GMP	Good Manufacturing Practice
HFA	Hydrofluoroalkane
hIL-33	Human interleukin-33
HR	Heart rate
ICF	Informed Consent Form

ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IP	Investigational product
IUD	Intrauterine devices
IUS	Intrauterine system
IV	Intravenous(ly)
LABA	Long-acting beta-2-agonists
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonists
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
n	Sample size or number of observations
NaCl	Sodium chloride
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
SABA	Short-acting beta agonists
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Subcutaneous
SD	Standard deviation
SOC	Standard of care
SOP	Standard operating procedure
SST	Serum separator tube

ST2	Surface receptor 2
$t_{1/2}$	Terminal half-life
TB	Tuberculosis
TEAE	Treatment emergent adverse event
Th2	T helper-2
t_{max}	Time to maximum observed concentration
US	United States
WOCBP	Women of childbearing 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 IL-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, food allergies, and atopic dermatitis.

2.1 Background Information

Asthma is a chronic immuno-inflammatory disease associated with significant morbidity and mortality and affects people from childhood to old age.[4] Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and leads to bronchoconstriction.[5]

The more severe forms of asthma are characterized by acute or subacute attacks and exacerbations leading to progressively worsening shortness of breath, coughing, wheezing, and chest tightness with a combination of systemic symptoms.

There are different forms (endotypes) of asthma and based on the pathogenic mechanisms asthma is generally subdivided into Th2 and non-Th2 asthma. A series of cytokines, associated with type 2 immune responses such as IL-5, IL-4, and IL-13 have been observed elevated in Th2 asthmatic patients.[6] These patients also tend to have high levels of circulating immunoglobulin E (IgE) and often present co-morbidities such as atopic dermatitis, food allergies, and allergic rhinitis. These conditions are considered to be interleaved and to share common pathogenic mechanisms and constitute the so called ‘atopic march’.[7] [8]

Normally patients with type 2 asthma also present with high levels of peripheral and lung eosinophils. Regardless of the asthma endotype, respiratory symptoms characterize asthmatic patients and worsening of symptoms or need to modify the current treatment indicate exacerbation. Exacerbations are also defined by worsening of lung functionality tested via spirometry and forced expiratory volume in 1 second (FEV_1), the most common parameter used to monitor airways obstruction in patients with asthma.

Current therapeutic management for asthma takes 2 approaches generally based upon empirical evidence rather than on targeting the underlying pathogenesis. Inhaled corticosteroids (ICS) over time open swollen airways; oral corticosteroids are required during an acute attack. Long-acting beta-2-agonists (LABA) are used to maintain disease control on a day to day basis, by providing prolonged bronchodilation. However, a substantial number of patients fail to gain clinical benefit from the standard treatments. Poor patient compliance may be a part of the reason for this lack of therapeutic benefit. Nonetheless, it is noteworthy that studies assessing asthma control reported persistent symptoms in over 20% of the patients, despite full treatment compliance.[4]

There are several classes of products available for use in patients with persistent asthma. These include, as mentioned above, ICS, inhaled long-acting beta-adrenergic agonists, as well as leukotriene modifying drugs and methylxanthines. Biologics (i.e. monoclonal antibodies) are also part of the approved medicines used to treat asthma patients. Omalizumab (Xolair®) targets IgE, a key pathogenic player in asthma, and was approved by the United States (US) Food and Drug Administration in 2003 for the treatment of moderate to severe allergic asthma. The European Medicines Agency also approved Xolair® in 2005 for use in adults, adolescents, and children (6 to <12 years of age) with convincing IgE mediated asthma. Recently, another biologic, mepolizumab (Nucala®), an anti IL-5 mAb (IgG1 kappa) has been approved as add-on maintenance treatment in patients with severe asthma aged 12 years and older and with an eosinophilic phenotype. In addition, reslizumab (Cinqair®), an anti IL-5 mAb (IgG4 kappa) was also approved with a more restricted profile i.e. only for patients aged 18 years and older with severe asthma and an eosinophilic phenotype.

Standard asthma therapies aim to give symptomatic relief for the disease without changing the underlying biology, whereas mAbs offer a new class of therapeutic agents, which have the potential to alter the course of the disease by interfering with specific aspects of the asthma pathogenic cascade. Studies which have focused on patients with severe asthma are ongoing with various mAbs targeting Th2 cytokines (i.e. IL-4, IL-5, and IL-13). These studies have shown significant clinical benefit. Moreover, approval of the anti IL-5 mAbs mepolizumab (Nucala®) and reslizumab (Cinqair®), stresses the further potential benefit in targeting Th2 cytokines.

Despite the success of these mAbs targeting Th2 cytokines, patients with severe asthma still represent a group of patients with a high medical need. New approaches based on the inhibitions of Th2 responses might therefore provide a novel and much needed new strategy. Interleukin-33 is centrally based on initiating, sustaining, and driving the effector phase of Th2 pathogenic responses. Interleukin-33 is known to modulate the function, expansion, and redistribution of eosinophils, a type of white cells often increased in the peripheral blood and lungs of asthmatic patients. Studies in animal models have demonstrated that inhibition of IL-33 controls this eosinophilia. Also in human subjects with a polymorphism of the IL-33 receptor (ST2), which confers protection from asthma, low levels of eosinophils have been observed in their periphery.

Interleukin-33 also potently activates innate lymphoid cell 2 (ILC2) to release cytokines such as IL-4, IL-13, and IL-5 which amplify the pathogenic Th2 response. ANB020 is a powerful and efficient inhibitor of IL-33, and thus ANB020 potentially offers an additional and novel treatment approach to treat severe patients who fail to respond to the current 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 [K_Ds] of 1 pM versus 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 ($t_{1/2}$) 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 mAb in the monkey.
- Multiple-dose, Good Laboratory Practice-compliant toxicology and toxicokinetic studies (4-week duration with an 8-week recovery phase and 13-week duration with an 8-week recovery phase) have been conducted with ANB020 administered by SC and IV injection to cynomolgus monkeys. These studies produced no significant test article-related effects and established a No Observed Adverse Effect Level of 50 mg/kg.

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 single ascending dose (SAD) and multiple ascending dose (MAD) study (ANB020-001) in healthy subjects is being performed. The SAD part of the study has been completed and 64 subjects were enrolled in the SAD part. Dosed cohorts in the SAD part included 10, 40, 100, and 300 mg SC and 40, 100, 300, and 750 mg IV (n=32 SC route, n=32 IV route). No significant changes in the vital signs (blood pressure [BP], heart rate [HR], or body temperature), physical examinations, or electrocardiograms (ECG) were noted. 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 upper respiratory infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (31% versus 27% in placebo and ANB020 group, respectively). One serious adverse event (SAE) of decreased neutrophils was reported in the ANB020 750 mg dose group which resolved without sequelae prior to study completion. This event was also considered a serious unexpected adverse reaction and was deemed possibly related to the study treatment. No other observations of decreased neutrophils lower than 1.5×10^9/L were observed. One subject in the ANB020 40 mg dose group, had an increased troponin level which returned to normal prior to study completion. No other significant changes in the laboratory test results were noted.

The PK and pharmacodynamic (PD) data obtained from the Phase I study (ANB020-001, SAD part) have been utilized to determine the route and dose of ANB020 to be used in this study. The PK data generated indicated that a linear PK profile was observed upon ANB020 administration across the dose ranges investigated, regardless of the route, but with less than dose-proportional increases in exposure for the SC dosing. The estimated ANB020 mean terminal $t_{1/2}$ ranged approximately 14 to 17 days. Persistent and nearly complete inhibition of ex vivo IL-33 stimulated INF-γ production in whole blood was observed following a single dose (except 10 mg SC) as soon as 24 hours, and lasting through 84 days (latest time point observed for 300 mg and 750 mg IV).

There were 32 subjects enrolled in the MAD part of the study (ANB020-001, MAD). Results from data will serve as the basis for the route of administration of ANB020 in future studies. The estimated ANB020 mean terminal $t_{1/2}$ in the MAD was approximately 17 days after SC injection and ranged from approximately 16 to 20 days with IV infusion.

2.2 Rationale

This proof of concept study is intended to explore the activity of ANB020 in adult patients with severe eosinophilic asthma. ANB020 is a highly efficient inhibitor of IL-33, a cytokine that is considered to drive the pathogenic cascade in asthma. Interleukin-33 directly effects eosinophil counts and function by acting in the early phases of the atopic immune response which is upstream of current asthma treatments with clinically validated targets such as IL-5, IL-4, and IL-13. The possibility to influence complementary and synergistic pathways involved in asthma pathogenesis, might provide a therapeutic improvement compared to the inhibition of single downstream pathways. This study will explore the effects of ANB020 300 mg/100 mL IV administration compared to placebo on validated endpoints such as eosinophilia, FEV_1, and fractional exhaled nitric oxide (FeNO).

2.3 Hypothesis

The purpose of this study is to explore the effects of ANB020 300 mg/100mL IV administration compared to placebo on eosinophilia, FEV_1, and FeNO in adult patients with severe eosinophilic asthma.

2.4 Risk-Benefit Assessment

A patient with eosinophilic asthma may or may not benefit from participating in this study. However, based upon the inhibition of IL-33 by the investigational product (IP) and pre-clinical study results, patients with eosinophilic asthma may benefit. Participation in this study may help to develop important scientific knowledge that could contribute to the development of a new medication and better comprehensive treatment of patients who suffer from asthma, atopic dermatitis, or 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) conducted 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 the Phase I study (ANB020-001), 64 healthy subjects were enrolled and dosed in the SAD part. The doses implemented in the SAD study were 10, 40, 100, and 300 mg SC and 40, 100, 300, and 750 mg IV. No significant changes in the vital signs (BP, HR, or body temperature), physical examinations, or ECGs were noted. The most commonly reported TEAEs were upper respiratory tract infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (31% versus 27% in placebo and ANB020 group, respectively). A total of 44% subjects in the placebo as well as ANB020 group had study drug related TEAEs. One SAE of decreased neutrophils was reported in the ANB020 750 mg dose group which resolved without sequelae prior to study completion. This event was also considered a serious unexpected adverse reaction and was deemed possibly related to the study treatment. No other observations of decreased neutrophils lower than 1.5×10^9/L were observed. One subject in the ANB020 40 mg dose group, had an increased troponin level which returned to normal prior to study completion. No other significant changes in the laboratory test results were noted.

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 mAb, based on clinical studies with other mAbs, 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, hypotension, 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 reduction of eosinophils (blood eosinophil count) from Baseline (Day 1 pre-dose) to Day 22 in adult severe eosinophilic asthma patients administered with ANB020.
- To assess the safety and tolerability of a single, IV dose of ANB020 compared to placebo in adult patients with severe eosinophilic asthma.

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To measure the reduction of eosinophils (blood eosinophil count) from Baseline (Day 1 pre-dose) to the End of Study (EOS) visit (Day 127) in adult severe eosinophilic asthma patients administered with ANB020.
- To assess the change from Baseline in the clinic FEV_1 from Baseline (Day 1 pre-dose) to the EOS visit (Day 127).
- To assess the change from Baseline in FeNO in the breath from Baseline (Day 1 pre-dose) to the EOS visit (Day 127).
- To assess the PD activity of ANB020 on ex vivo induced IFN-γ levels.
- To test for any immunogenicity to ANB020.
- To describe the limited PK of ANB020 following a single, IV dose in adult patients with severe eosinophilic asthma.

3.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- To assess the effect of ANB020 on circulating serum cytokines.
- To assess the activity of ANB020 after a single, IV dose on clinical scores such as the Asthma Control Questionnaire (ACQ), Patient Global Impression of Change (PGIC), and the Clinical Global Impression of Change (CGIC).

- To assess the effect of ANB020 on the asthma symptoms, change in standard of care (SOC) treatment, and rescue medication (short-acting beta-agonists [SABA]) usage.
- To assess the effect of ANB020 on IgE levels.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a Phase IIa, double-blind, placebo-controlled, proof of concept study designed to assess the effects of a single 300 mg/100 mL IV dose of ANB020 compared to placebo in adult patients with severe eosinophilic asthma. This study will also assess the safety and tolerability of ANB020 in adult patients with severe eosinophilic asthma.

A written informed consent will be obtained from each patient prior to completing any study procedures. At the Screening visit (7-14 days before Day 1) inclusion and exclusion criteria will be assessed. Medical history, ongoing medications, as well as vital signs will be recorded. Various other study assessments including a physical examination, FeNO measurement, spirometry to determine FEV_1, and laboratory tests will be performed (See Table 4.1 for study procedures and time points).

On Day 1, patients will present to the study center, and the inclusion and exclusion criteria will be verified. Eligible patients will be randomized to receive one IV dose of either ANB020 (300 mg/100 mL) or placebo (0.9% sodium chloride [100 mL]) in a 1:1 ratio. Specific study assessments (See Section 6.0) and safety laboratory tests (See Table 4.1) will be performed. Blood samples to determine eosinophil count (See Table 4.1), ex vivo induced IFN-γ levels, anti-drug antibodies (ADA), serum cytokines, and serial samples for PK analysis will be collected at specified time points (See Section 18.0). Patients will remain in the study center for approximately 6 to 8 hours to complete the study assessments. 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.

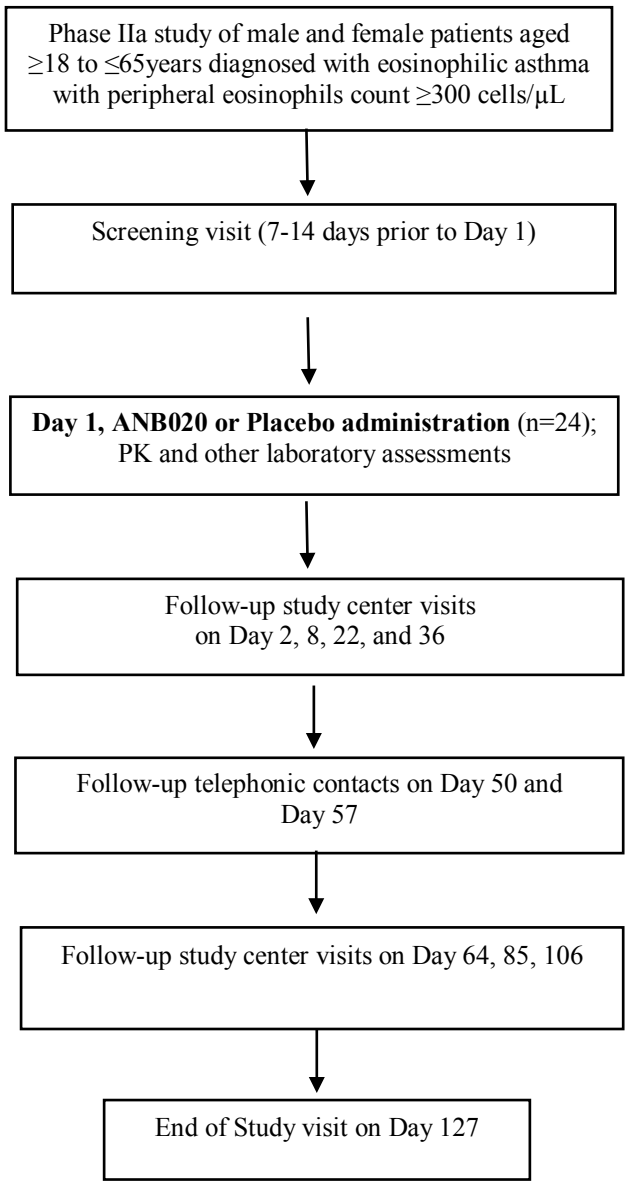
After completing the Day 1 assessments, all patients will be followed up period for 18 weeks. During the follow-up period, patients will return to the study center for study assessments on Day 2, 8, 22, 36, 64, 85, and 106 and will be contacted via telephone by study staff on Day 50 and 57 (See Table 4.1 for study procedures and time points). The EOS visit will be on Day 127 (Week 18) at the study center (See Table 4.1).

All patients will undergo FeNO and FEV_1 tests at each study center visit. An ACQ (See Section 13.0) will be completed by all patients at each study center visit except (Day 2) and the patient diary must be completed on a daily and weekly basis. The Investigator will rate the patient's response using the CGIC scale and the patients will be asked to rate the degree of change in the overall asthma status using the PGIC scale (part of the diary card [See Section 6.0

for description and Table 4.1 for instructions]). The PGIC and CGIC scales are presented in Section 14.0 and Section 15.0, respectively. During the follow-up period, other assessments including vital signs, safety laboratory testing, eosinophil count, PK, and biomarker analysis will be performed at specified time points (Table 4.1).

The study design is presented in Figure 4.1 and the Schedule of Events is presented in Table 4.1.

Figure 4.1 Schematic of Study Design for Protocol ANB020-004



Abbreviations: PK = pharmacokinetics; n = sample size

Table 4.1 Schedule of Events

Assessment Days	Screening *7-14 days prior to Day1*	Day 1	Day 2	Week 1 Day 8	Week 3 Day 22	Week 5 Day 36 (+/-2 days)	Week 7 Day 50 (Phone) (+/-2 days)	Week 8 Day 57 (Phone) (+/-2 days)	Week 9 Day 64 (+/-2 days)	Week 12 Day 85 (+/-2 days)	Week 15 Day 106 (+/-2 days)	Week 18 EOS Day 127/ET[g] (+/-2 days)
General Assessments												
Informed Consent	X[l]	X[a]										
Medical History/Demographics	X											
Inclusion/Exclusion Criteria	X	X[e]										
Clinical Observations												
Exhaled change in nitric oxide (FeNO)	X	X[e]	X	X	X	X			X	X	X	X
FEV_1 (Spirometry)[j]	X	X[e]	X	X	X	X			X	X	X	X
Patient and study staff completed: Asthma Control Questionnaire[j]	X	X[e]		X	X	X			X	X	X	X
Patient Diary[k]	X	X	X	X	X	X	X	X	X	X	X	X
Investigator's assessment (CGIC)[j]			X	X	X	X			X	X	X	X
Safety Assessments												
Physical Examination	X											X
Safety Laboratory[b]	X	X[e]	X	X	X	X			X	X	X	X
Hematology Panel for Eosinophils[c]	X	X[e]	X	X	X	X			X	X	X	X
Vital Signs	X	X	X	X	X	X			X	X	X	X
Urinalysis	X								X	X	X	X
Serum Pregnancy Test (WOCBP Only)[b]	X		X	X	X	X			X	X	X	X
Urine Pregnancy Test (WOCBP Only)		X[e]										
FSH[d]	X											
12-Lead ECG	X											X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X
Virology, TB screening, and Drugs of abuse screen	X[b]											
Samples for ADA[f]		X[e]		X		X				X	X	X

Assessment Days	Screening *7-14 days prior to Day1*	Day 1	Day 2	Week 1 Day 8	Week 3 Day 22	Week 5 Day 36 (+/-2 days)	Week 7 Day 50 (Phone) (+/-2 days)	Week 8 Day 57 (Phone) (+/-2 days)	Week 9 Day 64 (+/-2 days)	Week 12 Day 85 (+/-2 days)	Week 15 Day 106 (+/-2 days)	Week 18 EOS Day 127/ET[g] (+/-2 days)
PK/PD/Biomarker Assessments												
Samples for PK[f]		X	X	X	X	X			X			
Whole blood sampling for ex vivo induced IFN-γ [f]		X[e]										X
Serum Sampling for Biomarkers Cytokines[f] (IL-33, IL-4, IL-5, IL-9, IL-13, sST2)		X[e]	X	X	X	X			X			X
IP administration												
Administration of ANB020 or Placebo		X										

Abbreviations: ADA = anti-drug antibody; CGIC = Clinical Global Impression of Change ECG = electrocardiogram; EOS: End of Study; ET = Early Termination; FeNO = fractional exhaled nitic oxide; FEV_1 = forced expiratory volume in 1 second; FSH = follicle stimulating hormone; IL = interleukin; IFN-γ = interferon-gamma; IP = investigational product; PD = pharmacodynamics; PK = pharmacokinetics; TB = tuberculosis; WOCBP = women of childbearing potential

a Confirm informed consent and continued willingness to participate.

b See Table 7.1 for safety laboratory details (Virology, QuantiFERON® TB Gold test, and drugs of abuse to be performed at screening only). Serum pregnancy for WOCBP will be performed at all study center visits except Day 1. On Day 1, urine pregnancy test will be performed prior to IP administration.

c Sample for eosinophil count will be obtained as part of the standard hematology safety laboratory panel at each study center visit.

d The FSH levels will be obtained only on postmenopausal patients defined as aged over 45 years with at least 1 year of amenorrhea. Blood samples to determine the FSH levels will be obtained only at screening.

e Complete prior to IP administration on Day 1.

f See Section 18.0 (Appendix VI) for PK, IFN-γ, ADA, and biomarker cytokines collection time points. On Day 1, PK samples will be collected prior to IP administration as well as post-dose as specified in Section 18.0 [Appendix VI].

g ET visit will include all procedures to be done at EOS visit as well as any procedures that should be done at the next regularly scheduled visit (Please collect sample for PK analysis if the ET visit occurs between Day 1 to Day 64). ET visit will be performed if the patient discontinues the study before EOS visit. If the patient completes all study visits and return to study center for EOS visit on Day 127, ET visit will not be applicable.

h Patients with any ongoing AEs or SAEs at the time of scheduled discharge from the study center on Day 1 should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant.

i ACQ and CGIC scales must be completed prior to blood draw/lab assessments and other procedures such as FeNO, FEV_1 on each study center visit. On Day 1, the applicable scales and questionnaire must be completed prior to IP administration as well as prior to laboratory assessments and other study procedures.

j Both pre- and post-bronchodilator spirometry (FEV_1) should be performed at every clinic visit. Please refer to Section 6.1.2 for details.

k Patient Global Impression of Change (PGIC) scale will be a part of the patient diary card and the scale should be completed after receiving IP (i.e. after Day 1). Additional instructions will be provided in the patient diary card.

l Informed consent can occur prior to the -14 day Screening Visit. Note: consenting must occur prior to conducting any study procedures.

4.2 Discussion of Study Design

ANB020 is 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 PD activity in terms of cytokine modulation has been demonstrated in non-clinical and clinical studies, justifying its further development in patients with eosinophilic asthma.

Emergent data of the Phase I study (ANB020-001) in healthy subjects 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 the SAD part of the study, 64 subjects were enrolled and dosed. The doses implemented in the SAD part were 10, 40, 100, and 300 mg SC and 40, 100, 300, and 750 mg IV. No significant changes in the vital signs (BP, HR, or body temperature), physical examinations, or ECGs were noted. The most commonly reported TEAEs were upper respiratory tract infection (50% versus 48% in placebo and ANB020 group, respectively) and headache (31% versus 27% in placebo and ANB020 group, respectively). A total of 44% subjects in the placebo as well as ANB020 group had study drug related TEAEs. One SAE of decreased neutrophils was reported in the ANB020 750 mg dose group which resolved without sequelae prior to study completion. No other observations of decreased neutrophils lower than 1.5×10^9/L were observed. One subject in the ANB020 40 mg dose group, had an increased troponin level which returned to normal prior to study completion. No other significant changes in the laboratory test results were noted.

The dose of ANB020 selected for this study 300 mg/100 mL (IV) has provided complete inhibition of IL-33 induced cytokine release (ex vivo) up to 84 days and has been administered safely in study ANB020-001.

Eosinophilic asthma is a Th2 associated atopic disease. Patients with eosinophilic asthma have been demonstrated to have improved FEV_1 and reduced exacerbations when treated with anti-IL5 medications, which reduce eosinophil levels. Interleukin-33 is upstream of IL-5 in the Th2 cytokine cascade. Inhibition of IL-33, through the use of ANB020, would be expected to reduce IL-5, as well as other Th2 inflammatory mediators (such as IL-4 and IL-13 also successfully targeted in Th2 asthma), resulting in reduced asthma symptoms and eosinophil levels and improved lung function.

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 aged ≥18 to ≤65 years and able to give informed consent.
- Patients with a confirmed clinical diagnosis of eosinophilic asthma with peripheral eosinophils count ≥300 cells/μL at screening.
- Twelve months history of diagnosis of eosinophilic asthma (with asthma exacerbation within the last 12 months [before screening] requiring rescue medication).
- Severe asthma diagnosed according to the Global Initiative for Asthma (GINA) 2016 requiring GINA treatment steps 3 to 5 (See Section 16.0).
- Pre-bronchodilator FEV_1 of <80% at screening.
- Body mass index (BMI) of 18 to 38 kg/m^2 (inclusive) and total body weight >50 kg (110 lb.). BMI = weight (kg)/(height [m^2]).
- Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1 and be using highly effective methods of contraception (See Section 4.3.4) or be surgically sterile, or be postmenopausal throughout the study and for 18 weeks after the last dose of IP administration. Postmenopausal patients defined as (1) aged over 45 years with at least 1 year of amenorrhea and levels of follicle-stimulating hormone (FSH) over 20 IU/L at screening or (2) aged over 50 years with at least 1 year of amenorrhea.
- Male patients must be willing to use effective methods of contraception during the entire study period and for 18 weeks after the last dose of IP administration (See Section 4.3.4).
- Patient must be on high dose ICS plus LABA (See Section 5.8.2 for high dose guidelines). Systemic corticosteroids (intramuscular or oral) up to the equivalent of 15 mg/day prednisone will be allowed.
- Willing and able to comply with the study protocol requirements.
- Have the ability to read and understand the study procedures and can communicate meaningfully with the Investigator and staff.

4.3.2 Exclusion Criteria

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

- Have concomitant medical condition(s) which may interfere with the Investigator's ability to evaluate the patient's response to the IP.
- Have experienced severe life-threatening anaphylactic reactions.
- Have received any IP within a period of 3 months or 5 half-lives of an IP (whichever is longer) before screening (this also includes investigational use of marketed products).
- Have received high dose systemic corticosteroids (equivalent to >15 mg/day prednisone), nonsteroidal, immunosuppressant, or immunomodulating treatments within 8 weeks before screening.
- Have received treatment with biologics such as mepolizumab or omalizumab within 3 months or 5 half-lives (whichever is longer) before screening.
- Abnormal ECG assessment at screening (any abnormality that the Investigator believes is not safe for study participation).
- Uncontrolled hypertension, or acute ischemic cardiovascular diseases.
- Have received antibiotic treatment within 4 weeks before screening.
- Have a history of hypersensitivity or allergic reactions to polysorbate 80, a component of the ANB020 formulation or the inactive ingredients (excipients).
- If female, is pregnant or lactating, or intend to become pregnant during the study period.
- History (or suspected history) of alcohol or substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition) Substance Use Disorders guidelines within 2 years before screening.
- Current smokers or former smokers with a smoking history of ≥15 pack years. If a patient has less than 15 pack years smoking history, he or she should have quit smoking at least 6 months before screening to enroll in the study.
- Positive blood screen for hepatitis C virus antibody, hepatitis B virus surface antigen, human immunodeficiency virus 1 and 2 antibodies, or *Mycobacterium tuberculosis* (TB). Patients with an indeterminate QuantiFERON® TB Gold result at screening will be allowed one retest; if not negative on retesting, the patient will be excluded.
- Any co-morbidity that the Investigator believes is a contraindication to study participation. This includes, but not limited to any respiratory (e.g. pulmonary fibrosis, eosinophilic granulomatosis with polyangiitis [EGPA], allergic bronchopulmonary aspergillosis [ABPA]), cardiovascular, gastrointestinal, hematological, neurological,

immunological, musculoskeletal, renal, infectious, neoplastic, or inflammatory condition that may place the safety of the subject at risk during the study, influence the results of the study or their interpretation, or prevent the patient from completing the entire duration of the study.

- Have any other physical, mental, or medical conditions which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
- Receipt of a live attenuated vaccine within 4 weeks before screening.
- Planned surgery during the study or 30 days before screening.
- 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

Adult patients (age ≥18 to ≤65 years) with a confirmed clinical diagnosis of eosinophilic asthma with a documented blood eosinophil count of ≥300 cells/μL despite receiving SOC treatment.

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 5.8.
- Restricted alcohol intake (<28 units per week).
- Strenuous exercise should be avoided up to 72 hours before the planned study visits.
- WOCBP must follow a consistent and correct use of highly effective methods of birth control during the study period and for 18 weeks after the last dose of IP administration.
- Male patients must be willing to use contraception throughout the study and for 18 weeks after the last dose of IP administration which includes a total of 5 half-lives of the IP (estimated to be approximately 70 days) plus an additional 50 days (which includes the duration of sperm turnover) post treatment completion. Additionally, female partners of male patients must also use highly effective methods of contraception if she is a WOCBP.

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 include oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine systems (IUS) such as Mirena®.
- Non-hormonal intrauterine devices (IUDs)
- Bilateral tubal ligation
- Vasectomy

Acceptable alternate methods of highly effective contraception must be discussed with the Investigator to ensure highly effective methods of contraception are instituted prior to the 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 Restrictions Prior to Lung Function Assessments

- Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments.
- Patients should avoid eating a large meal for at least 2 hours prior to all lung function assessments.

4.3.5 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 inclusion and exclusion criteria are to be followed explicitly. If a patient who does not meet the enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study. AnaptysBio and IQVIA

must be contacted, and if the patient has received ANB020 or placebo, the patient must be followed up until EOS (Day 127) for any AEs and/or SAEs.

In addition, the patients will be withdrawn from the study under the following circumstances:

- Prior to IP administration, the Investigator decides that the patient should be withdrawn or is at risk. If this decision is made because of an AE or a clinically significant laboratory value, the IP should not be administered and appropriate measures are to be taken. AnaptysBio and/or IQVIA 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 participant's best interest.

Patients who discontinue the study early will have early termination (ET) procedures performed as shown in Table 4.1 (Schedule of Events).

Patients who are withdrawn from the study after Day 36 will not be replaced. All patients who discontinue the study prior to completing the Day 36 study assessments will be replaced. The study pharmacist should also be notified of any patient who has received IP and discontinues prior to Day 36.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

ANB020 is a humanized IgG1/kappa 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)-XEL^{TM} system to achieve a desired functional inhibitory potency.

ANB020 will be administered to patients by IV infusion in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with sterile normal saline (0.9% sodium chloride [NaCl]). Placebo will be administered by IV infusion as 100 mL sterile normal saline (0.9% NaCl). Infusions will be administered over 1 hour.

5.2 Identity of Investigational Product

ANB020 is manufactured by Patheon of Greeneville, North Carolina, US under Good Manufacturing Practice (GMP) regulations. ANB020 is provided as a sterile clear to slightly opalescent solution in a glass vial for IV infusion and contains no preservatives.

The ANB020 vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. 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 single-use only; therefore, any remaining solution should be discarded.

The placebo contains no active drug and will be sterile normal saline (0.9% NaCl) for infusion. The placebo will be procured from the pharmacy stock supply.

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 1	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 randomized, double-blind, placebo-controlled study. On Day 1, after verification that all inclusion and no exclusion criteria have been met, the patients will be randomized in a 1:1 ratio to ANB020 or placebo. As patients become eligible they will be assigned randomization numbers which will be used to assign the allocated treatment. The Sponsor, Investigator, and patients will be blinded to treatment assignment of ANB020 or placebo. Additional information can be found in the study manuals.

5.5 Selection of Doses in the Study

A single IV infusion of 300 mg/100 mL of ANB020 or 100 mL placebo (0.9% NaCl) will be administered.

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

5.6 Selection and Timing of Dose for Each Patient

Patients will receive a single dose of ANB020 or placebo administered under supervision at the study center. The infusion will be administered at the rate of 100 mL per hour 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. Infusions will be administered over 1 hour. The ANB020 or placebo infusion may be slowed or interrupted for patients experiencing infusion-related AEs.

5.7 Blinding/Unblinding

5.7.1 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. The IP and placebo will be identical in physical appearance. The Sponsor, Investigator, and patients will be blinded to treatment assignment of ANB020 or placebo. The unblinded pharmacy staff will be provided the randomization assignments to prepare the assigned IP for each patient.

5.7.2 Unblinding

The investigator is responsible for ensuring treatment-blinding information is maintained for all subjects. Unblinding information is available at the site by the unblinded pharmacist and investigator in case of a medical emergency.

Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary to know what treatment the subject received. If the investigator deems identification of the study drug is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (ANB020 or placebo) will alter subsequent care, the treatment code for the specific subject will be obtained. Prior to unblinding, the investigator or appropriate designee should attempt to contact the Sponsor's Medical Monitor to discuss the need to unblind a subject. In the event the Medical Monitor cannot be reached, the investigator should ensure that the unblinding of the treatment code is performed in a discrete manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. The investigator should contact the Sponsor's Medical Monitor immediately (within 24 hours including weekends) following emergency unblinding. Once the subject's treatment assignment has been obtained in the event of an emergency, the date, time, and reason for the unblinding must be recorded in the pharmacy log, on the subject's CRF and source notes and signed by the investigator.

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 deviation and should be recorded in the electronic case report form (eCRF).

- Treatment with systemic corticosteroids (intramuscular or oral) equivalent to >15 mg/day prednisone, nonsteroidal, immunosuppressant or immunomodulating drugs within 8 weeks before screening and throughout the study.
- Any antibiotic treatment within 4 weeks before screening.
- Use of biologics such as mepolizumab or omalizumab within 3 months or 5 half-lives (whichever is longer) before screening and throughout the study.
- Any live attenuated vaccine within 4 weeks of screening and for the duration of the study (Day 127).

5.8.1.1 Excluded Medications Prior to Lung Function Assessments

Patients should withhold their usual asthma therapies prior to the lung function tests on the study visit days.

- Short-acting bronchodilators (e.g. albuterol [salbutamol] or ipratropium) should be withheld for at least 6 hours before spirometry.
- Twice daily long-acting bronchodilator (LABA or long-acting muscarinic antagonist [LAMA] containing therapies) should be withheld for 12 to 24 hours and once daily long-acting bronchodilator (LABA or LAMA containing therapies) for >24 hours before spirometry.
- Leukotriene receptor antagonists (LTRA) should be restricted for >24 hours.
- Twice daily theophyllines should be withheld for at least 12 to 24 hours and once daily theophyllines for >24 hours before spirometry.
- If a patient has taken rescue SABA within 6 hours of the planned spirometry study center visit, they should either:
    a. remain at the center until the 6-hour withholding time has been reached or
    b. return on the following day for lung function assessments (If the patient completed Day 22 visit, he or she can return within 2 days [allowed window period per protocol] for the lung function assessment).

5.8.2 Allowed Medications

Use of high dose ICS plus LABA and systemic corticosteroids (intramuscular or oral) up to the equivalent of 15 mg/day prednisone will be allowed in the study.

High dose guidelines are as follows:

- Beclomethasone dipropionate (chlorofluorocarbon [CFC]) High: >1000 µg
- Beclomethasone dipropionate (hydrofluoroalkane [HFA]) High: >400 µg
- Budesonide (dry powder inhaler [DPI]) High: >800 µg
- Ciclesonide (HFA) High: >320 µg
- Fluticasone furoate (DPI) High: 200 µg
- Fluticasone propionate (DPI or HFA) High: >500 µg
- Mometasone furoate High: >440 µg

- Triamcinolone acetonide: >2000 µg

Specific treatment for asthma exacerbations will be allowed at the Investigator's discretion. Oral prednisolone and or antibiotics will be allowed at the discretion of the treating physician.

Administration of the inactivated flu vaccine will be allowed. Females of childbearing potential are to continue using their hormonal contraceptives and postmenopausal women are allowed to use hormone replacement therapy.

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 for the EOS (Day 127) or ET visit for final safety and EOS assessments. After this visit, 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 30 days after the EOS visit should be reported to the safety team at IQVIA and followed up until final outcome or stabilization.

5.10 Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any deviations from the intended regimen must be recorded in the eCRF. Infusion start date/time and infusion end date/time will be documented in the patient's eCRF. Any infusion interruptions (stop date/time and restart date/time) and/or incomplete dose administration will also be documented.

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 IQVIA/AnaptysBio by the Investigator or may be destroyed on site following institutions standard operating procedures (SOPs) and proper accountability by IQVIA

site monitor. The Investigator is not permitted to return or destroy unused IP supplies or packaging materials unless authorized by IQVIA.

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; however, a window period of +/-2 days can be implemented following the Day 22/Week 3 visit.

There are visits where the protocol requires more than one procedure to be completed at the same time point. When indicated, the procedure must follow specific order of events, refer to Section 6.2.6 for instructions.

Study team must verify that patients withheld their usual asthma therapies prior to the lung function tests on each study center visit day. See Section 5.8.1.1 for the details.

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. Vital signs, physical examinations, medical history, and ongoing medications will be recorded. Other screening procedures will be carried out in accordance with the Schedule of Events in Table 4.1.

6.1.1 Fractional Exhaled Nitric Oxide (FeNO) Test

Measurement of FeNO will be performed at the time points indicated in Table 4.1 and in accordance with the guidelines published by American Thoracic Society/European Respiratory Society (ATS/ERS).[9] The FeNO test must be performed before the spirometry testing. Details about the FeNO measurement are provided in the pulmonary function testing manual provided by the manufacturer.

6.1.2 Spirometry (FEV_1 Measurement)

Spirometry will be performed at the time points indicated in Table 4.1 and according to the ATS/ERS guidelines.[10] The spirometer should be calibrated per ATS/ERS guidelines prior to the start of the lung function assessment on each study center visit day. The spirometer should be set to use the Global Lung Function Initiative reference equations.

Both pre- and post-bronchodilator spirometry should be performed at all clinic visits. Pre-bronchodilator spirometry will be performed after appropriate bronchodilator withholding period

(See Section 5.8.1.1) in the morning and post-bronchodilator spirometry will be performed 30 minutes following the administration of 400 µg salbutamol via a Volumatic.

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

6.1.3 Asthma Control Questionnaire

The ACQ (See Section 13.0) will be used in this study to assess the asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and SABA usage) along with the FEV_1 measurement.

Patients will be asked to recall their experiences during the previous week by responding to 5 symptoms related questions and 1 question related to bronchodilator use. Questions will be scored from 0 (totally controlled) to 6 (severely uncontrolled). The questionnaire will be completed at each study center visit except Day 2 visit (See Table 4.1) and must be completed prior to blood draw/laboratory assessments and other procedures such as FeNO and FEV_1. Refer to section 6.2.6 and Table 4.1 for timings and instructions.

6.1.4 Patient Diary

The patient diary will be distributed during each study center visit day (except EOS visit) and all patients will be trained to record the asthma symptoms and other details in the diary on a daily and weekly basis as listed below. All patients will be asked to return the diary cards when they come for the next study center visit and the study team will review the patient diary cards (from previous weeks) during each study center visit for completeness. (If the patient does not meet inclusion/exclusion criteria the diary card will not be collected).

The following details will be recorded in the patient diary on a daily and weekly basis.

Daily Recording

- Number of puffs that the patient needed to use their rescue (SABA) medication during the day.

Weekly Recording

- List asthma symptoms experienced during the week: wheezing, cough, shortness of breath, chest tightness, or describe other.
- Change in SOC treatment.
- Study treatment efficacy (after Day 1).
- Level of satisfaction with the side effects related to the study treatment (after Day 1).
- PGIC (after Day 1).
- Hospitalization due to asthma.

6.2 Study Day Procedures

6.2.1 Blood volume

The total blood volume for each patient will be approximately 295.5 mL, and within the National Institute of Health allotted amounts of 550 mL in any 8-week period.

6.2.2 Day 1 (Randomization)

On Day 1, study staff will confirm the informed consent and patient's willingness to participate in the study. The patients will be randomized to receive either ANB020 or placebo in a 1:1 ratio (12 patients will receive ANB020 and 12 patients will receive placebo). Additional Day 1 procedures will be carried out in accordance with the Schedule of Events in Table 4.1.

Patients will be allowed to leave the study center 6 to 8 hours after the ANB020/placebo administration 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 study center with the authorization of the Investigator or appropriately qualified delegate.

6.2.3 Follow-up Period

After completing the Day 1 assessments, all patients will be in the follow-up period for 18 weeks. During the 18-week follow-up period, the patients will return to the study center for various assessments on Day 2, 8, 22, 36, 64, 85, and 106 and will be contacted via telephone by

study staff on Day 50 and 57. The study procedures will be carried out in accordance with the Schedule of Events in Table 4.1.

6.2.3.1 Patient Global Impression of Change (PGIC)

The PGIC scale (See Section 14.0) will be used for an overall evaluation of response to treatment. The patient will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, i.e. Day 1. A 7-point rating scale will be used as listed below:

1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no changes, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

Refer to Table 4.1 for instructions.

6.2.3.2 Investigator's Assessment-Clinical Global Impression of Change (CGIC)

The CGIC scale (See Section 15.0) will be used for an overall evaluation of response to treatment. The Investigator will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, i.e. Day 1. A 7-point rating scale will be used as listed below:

1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no changes, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

The CGIC should be completed prior to blood draw/laboratory assessments and other procedures such as FeNO and FEV_1. The time points are indicated in the Schedule of Events in Table 4.1. Refer to section 6.2.6 and Table 4.1 for timings and instructions.

It is recommended that the same Investigator/Sub-Investigator completes the scale for all time points for a given patient.

6.2.4 End of Study

All patients will return to the study center for the EOS visit on Day 127 (Week 18). The EOS procedures will be carried out in accordance with the Schedule of Events in Table 4.1.

6.2.5 Early Termination

Patients who discontinue the study early will be asked to return to the study center for the ET procedures as shown in the Schedule of Events (Table 4.1). The ET visit will include all procedures to be done at EOS visit as well as any other laboratory assessment (PK or ADA) planned at the originally scheduled follow-up visit.

6.2.6 Timing of Procedures

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

- All safety assessments will be timed and performed relative to the start of IP administration.
- Blood draw: Lab-flow document should be followed for standardized order of blood draw collection. If entire panel is unable to be collected, hematology panel (eosinophils) will take precedence over other tests.
- Study specific scales and questionnaire forms should be completed prior to blood draw/laboratory assessments and other procedures such as FeNO, FEV_1.
- FeNO must be performed before FEV_1.

On Day 1, ACQ, safety laboratory tests, urine pregnancy (confirm negative), ADA, IFN-γ, cytokines, FeNO, and FEV_1 (both pre- and post-bronchodilator) must be completed prior to IP administration. The PK samples will be collected prior to IP administration as well as post-dose on Day 1. Refer to Table 4.1 (Schedule of Events) and Section 18.0 (Appendix VI) for additional details.

7.0 SAFETY, PHARMACODYNAMIC, AND PHARMACOKINETIC 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.

7.1.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study 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 IP. 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 screening (after informed consent), treatment, or follow-up period are to be recorded on the appropriate pages in the eCRF (either 'serious' or 'non-serious'). The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, and relationship to the IP. Each event should be recorded separately. All AEs that occur within 30 days after the patient's last visit (EOS visit) should also be reported.

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 IP, 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 IQVIA 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 IQVIA Safety:

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

The following are the Investigator's 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 respective 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 or recording the details of the outcome of the SAE on the appropriate eCRF, as well as any other details which may be requested by AnaptysBio and/or IQVIA in a timely manner**:**
    - Hospital records.
    - Medical records.
    - 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, please call IQVIA Safety Group (contact information is located on the SAE form), in addition to entering the SAE details in the eCRF.
    - The SAEs should continue to be reported for at least 5.5 half-lives of IP following last dose. Any significant AE which in the opinion of the Investigator is related to the IP, SAE, or pregnancy occurring within 30 days after the EOS visit and should also be reported to the safety team of IQVIA and followed up until outcome.
    - 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 recorded on the appropriate eCRF and must 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 IQVIA 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 IQVIA to the regulatory authorities as applicable, and to all participating Investigators as a 7-Day report. IQVIA will ensure that all SAEs are reported to the appropriate regulatory authorities.

Investigators will be notified by IQVIA of all SAEs that require prompt submission to their Independent Ethics Committee (IEC). Each Investigator must notify the IEC responsible for reviewing the study at their site of all 15-Day or 7-Day safety reports required by local regulations or IEC requirements and should provide written documentation of IEC notification for each report to IQVIA. This study will comply with all local regulatory requirements and adhere to the full requirements of International Council for Harmonisation (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 the time of informed consent signed 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 within 30 days after the patient's last visit should also be reported to AnaptysBio and/or IQVIA.

7.1.2 Clinical Laboratory Evaluations

Blood samples for the study-specific assessments will be collected at the visits specified in Table 4.1 (Schedule of Events) and Section 18.0 (Appendix VI) for the biomarker cytokines, ADA, INF-γ, and PK. A list of specific clinical laboratory evaluations is provided in Table 7.1 below:

Table 7.1 Clinical Laboratory Parameters

Hematology	**Clinical Chemistry**	**Virology** ***(Only at Screening)***	**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 (Absolute and %) Eosinophils (Absolute and %) Monocytes (Absolute and %) Neutrophils (Absolute and %) Lymphocytes (Absolute and %) Immunoglobulins (IgA, IgG, IgM, IgE, and IgD)	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) Sodium Troponin Urea **WOCBP Only** - hCG levels Postmenopausal woman aged over 45 years with at least 1 year of amenorrhea only - FSH levels (*only at Screening visit*)	Hepatitis B Surface Antigen Hepatitis C Antibody HIV Antibodies **TB Screening** QuantiFERON® TB Gold test	Bilirubin Blood Glucose Ketones Leukocytes Nitrates pH Protein Specific gravity Urobilinogen **At discretion of Investigator based on urinalysis results** Microbiology Urine Microscopy Urine Pregnancy-dipstick (Day 1 prior to IP administration)	Amphetamines Barbiturates Benzodiazepines Cocaine Marijuana/Cannabis Methadone Methamphetamine/ Ecstasy Morphine/Opiates Phencyclidine Tricyclic Antidepressants

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin hormone; HIV = human immunodeficiency virus; IP = investigational product; TB = tuberculosis; WOCBP = women of childbearing potential, % = percentage.

The central laboratory tests will be conducted by Q^2 Solutions, at multiple locations such as:

The Alba Campus Rosebank Livingston West Lothian
EH54 7EG Scotland, United Kingdom
Phone: [redacted]
Fax: + [redacted]

Quest House 125-135
Staines Road, Hounslow TW3 3JB, United Kingdom
Phone: [redacted]
Fax: + [redacted]

1600 Terrell Mill Road, Suite 100, Marietta
GA 30067, United States of America
Phone: [redacted]
Fax: + [redacted]

27027 Tourney Road, Valencia,
CA 91355, United States of America
Phone [redacted]
Fax: + [redacted]

The clinical laboratory test results will be reviewed for 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.

Serum samples for ADA determination will be collected on Days 1, 8, 36, 85, 106, and 127 (EOS)/ET according to the schedule presented in Section 18.0 (Appendix VI). 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. Analytical method to measure the ADA will be described in a separate bioanalytical report.

7.1.3 Vital Signs, Physical Findings, and Other Safety Assessments

Vital signs will be measured, and physical examinations and ECGs will be performed at the time points indicated in the Schedule of Events (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 the 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.

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 IP toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

7.2 Pharmacodynamics

Blood samples to determine the eosinophil count will be obtained as part of the standard hematology safety laboratory panel at screening, Day 1, 2, 8, 22, 36, 64, 85, 106, and 127/ET (See Table 4.1 and Table 7.1).

Blood samples will be taken in a serum separator tube (SST) to measure circulating cytokines including, but not limited to IL-4, IL-5, IL-9, IL-13, IL-33, and sST2 (See laboratory flowchart for detailed collection and processing instructions). Samples will be collected according to the schedule presented in Section 18.0 (Appendix VI).

Blood samples for ex vivo induced IFN-γ assessment will be collected in a sodium heparin tube (See laboratory flowchart for detailed collection and processing instructions). Samples will be collected according to the schedule presented in Section 18.0 (Appendix VI). 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 serum 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 of whole blood will be obtained in a Vacutainer® SST for the determination of ANB020 in human serum. Samples will be collected according to the schedule presented in Section 18.0 (Appendix VI).

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 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. Only the samples within the known stability of ANB020 at the time of receipt by the bioanalytical laboratory will be analyzed.

7.4 Efficacy

Efficacy assessments include FEV_1 and FeNO test results; clinical scores of ACQ, PGIC, and CGIC; patient diary data, and IgE levels.

Refer to Section 6.0 for more details about efficacy variables.

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), Q^2 Solutions and IQVIA are responsible for implementing and maintaining quality assurance and quality control systems with written 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 IQVIA/Q^2 Solutions 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, IQVIA, to perform all monitoring functions within this clinical study. IQVIA's monitors will work in accordance with

IQVIA's SOPs. 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 IQVIA.

Electronic data capture 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 current 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 IQVIA 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 IQVIA using statistical analysis system (SAS®), (SAS Institute, Cary, North Carolina, US) Version 9.2 or higher. IQVIA's 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 statistical analysis plan (SAP) that will be prepared and signed off prior to database lock. Any change to the data analysis methods will be documented in the 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

The number of patients to be enrolled is not based on statistical power considerations.

A total of approximately 24 patients will be randomized in a 1:1 ratio to receive ANB020 or placebo.

All patients who discontinue the study prior to completing the Day 36 study assessments will be replaced. Patients who are withdrawn from the study after Day 36 will not be replaced.

9.1.1 Analysis populations

Randomized Analysis Set

All patients who have been allocated to a randomized treatment arm, regardless of whether they received the planned treatment or not. Patients in this set will be analyzed in the respective randomized treatment arm.

Full Analysis Set

All patients who have received ANB020 or placebo and have at least one post-baseline blood eosinophils count assessment (Day 2). The full analysis set will be used for all efficacy analyses.

Safety Analysis Set

All patients who have received ANB020 or placebo. The safety analysis set will be used for all safety analyses. Patients in this set will be analyzed in the treatment arm that they actually received.

Pharmacokinetics Analysis Set

All patients who have received ANB020 and have at least one post-dose serum concentration data available for ANB020 without any events or protocol deviation deemed to affect PK assessments. The PK analysis set will be used for all PK analyses.

Pharmacodynamics Analysis Set

All patients who have received ANB020 or placebo and provide at least one evaluable post-dose PD measurement without any events or protocol deviation deemed to affect PD assessment. The PD analysis set will be used for all PD analyses.

9.2 Patient Disposition

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, enrolled, assigned treatment, 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 to categorize as major or minor and the same will be reported.

9.3 Patient Characteristics and Concomitant Medications

Patient characteristics 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 (n, 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.

9.4 Safety analyses

Following are the safety and tolerability endpoints:

- Assessment of AEs/SAEs (potentially significant and clinically important AEs, SAEs, and AEs leading to withdrawal).
- Physical examination.

- Vital signs.
- Clinical safety laboratory tests (hematology, biochemistry, immunoglobulins, and urinalysis).
- Electrocardiograms.
- Number of asthma exacerbations.
- Assessment of immunogenicity (ADA levels).

9.4.1 Adverse Events

Adverse events will be coded using the current MedDRA. For each treatment, numbers of events and percentage will be tabulated by Preferred Term and System Organ Class. The AEs, SAEs, AEs leading to treatment discontinuation, and AEs leading to withdrawal of patient will be tabulated for each treatment period.

Summaries over System Organ Class, Preferred Term 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. Summaries will also be presented by relatedness to IP and the severity of the AE.

9.4.2 Vital Signs Measurements, Physical Findings, and Clinical Laboratory Evaluations

Summaries and listings of vital signs, physical examination, ECG, and laboratory test results 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, listings 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, laboratory test results, and ECG results. Change from Baseline will also be summarized for vital signs measurements and clinical laboratory test results.

Number of asthma exacerbations will be summarized using frequency count and percentage. Time (in days) from randomization to the first asthma exacerbation will be used as a supportive variable and will be calculated as follows:

Start date of first asthma exacerbation − Date of randomization + 1.

The time to first asthma exacerbation for subjects who do not experience an asthma exacerbation during the period till end of study will be censored at the date of their last visit, or at the time point after which an exacerbation could not be assessed (for lost to follow-up patients).

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment delays the time to first exacerbation compared with placebo. A cox proportional hazard model will be deployed by using treatment group as a class variable and number of exacerbations in the study as covariates. Results of the analysis will be summarized as hazard ratios and 95% confidence intervals (CIs) comparing ANB020 with placebo.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot. The median time to event will be summarized by treatment, if there is sufficient uncensored data available to calculate these median values.

Analyses of ADA will be performed similar to the PD endpoint analysis as describe in Section 9.7.

9.4.3 Missing Data

No imputation will be performed for the missing data.

9.5 Efficacy analysis

The secondary efficacy variables (change in FEV_1 and change in FeNO), and exploratory variables (change in clinical scores for ACQ, PGIC, and CGIC, and applicable diary assessments) will be analyzed using the full analysis set.

For secondary efficacy endpoint, actual and change in FEV_1 from Baseline (Day 1) to the EOS visit (Day 127) will be summarized using descriptive statistics. Change from Baseline will be compared between ANB020 and placebo using a mixed-effect analysis of covariance (ANCOVA). This model includes, fixed effect as treatment, baseline efficacy variable levels as covariates, and patient as a random effect. Appropriate covariance structure will be used. Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI.

Supportive analyses will be performed using a mixed-model repeated measures (MMRM) analysis. The model includes terms for treatment, time point of measurement, and treatment by time point interaction as fixed effects and Baseline value (pre-dose measurement at randomization [Day 1]) as covariate. At each visit day, ANB020 will be compared with placebo and model-based least squares means for the treatment effects, 95% CIs, and p-values will be calculated for within and between treatment comparisons.

Other secondary efficacy endpoint and applicable exploratory endpoints analyses will be performed same as FEV_1 analyses.

9.6 Pharmacokinetic Analyses

9.6.1 Evaluation of Pharmacokinetic Data

The PK parameters will be derived using non-compartmental methods. The actual elapsed sampling times will be used in the PK parameter calculations. The PK analyses will follow Q^2 Solutions/IQVIA SOPs, unless otherwise specified.

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

- Maximum observed concentration (C_{max}).
- Time to maximum observed concentration (t_{max}).

Additional PK parameters may be determined if deemed appropriate.

9.6.2 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 nominal time point using the number of observations (n) and number of observations ≥lower limit of quantification, arithmetic mean, SD, coefficient of variation (CV), minimum, median, and maximum.

Graphs of mean and individual concentration-time data will be generated, as appropriate, and will be described in detail in the SAP.

9.6.3 Pharmacokinetic Parameter Data Analyses

Pharmacokinetic parameters will be listed and summarized, as appropriate using n, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV defined as

$$100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$$

where ‘s’ is the SD of the data on a log scale, except that t_{max} 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

Observed and change from Baseline for the eosinophil count, serum cytokines, and ex vivo induced IFN-γ will be listed and summarized descriptively by nominal time point and treatment. Baseline will be the last assessment before IP administration.

Comparison between ANB020 and placebo will be performed using a MMRM analysis with terms for treatment, time point of measurement, and treatment by time point interaction as fixed effects and Baseline value (pre-dose measurement at randomization [Day 1]) as a covariate. Appropriate correlation matrix will be used. Treatment differences will be presented with corresponding p-values for the test of no difference and 95% CI. Suitable transformations may be applied as appropriate. Graphical summaries will be generated, as appropriate.

The relationship between ANB020 concentrations and PD endpoints will be explored graphically. Further analysis details will be described in the SAP.

9.8 Interim Analyses

No interim analysis is planned for this study.

10.0 ETHICS

10.1 Independent Ethics Committee

An 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 IQVIA 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 IQVIA 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.

IQVIA or representative will handle the distribution of any of these documents to the national regulatory authorities.

IQVIA's 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. IQVIA 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 ICF 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.

10.5 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an IEC, or regulatory authority elects to terminate or suspend the study (due to such events as, but not limited to new information becomes available that may negatively impact patient safety, IP integrity, withdrawal of IND), a study-specific procedure for ET or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

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** IQVIA Customer Safety Services Global Data & Safety Monitoring 5927 S. Miami Blvd. Morrisville, NC 27560 United States
Clinical Study Supply Management Investigational Product AnaptysBio Inc. 10421 Pacific Center Ct Suite 200 San Diego, CA 92121 United States	**Clinical Study Supply Management Other than Investigational product** IQVIA 10188 Telesis Court, Suite 400 San Diego, CA 92121 United States
Data Management IQVIA Data Management Etamin Block (Building B3) Prestige Technology Park II Sarjapur-Marathalli Outer Ring Road Bangalore - 560103 India	**Biostatistics** IQVIA 12th Floor, G-Corp Tech Park Ghodbunder Road, Kasarwadawli, Thane (West) Thane - 400 607 India
Study Monitoring IQVIA 10188 Telesis Court, Suite 400 San Diego, CA 92121 United States	**Medical Writing** IQVIA 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 Ct Suite 200 San Diego, CA 92121 United States	**Central Laboratory** Q^2 Solutions Multiple locations

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 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, IQVIA, 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 Sub-Investigators, 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 representative (Section 17.0). 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.

[3] Nabe, T. Interleukin (IL)-33: New Therapeutic Target for Atopic Diseases. J. Pharmacol Sci. 2014;126:85-91.

[4] Nanzer AM, Menzies-Gow A. Defining severe asthma-An approach to find new therapies. European clinical Respiratory Journal. 2014;1:1-9.

[5] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available from: www.ginasthma.org.

[6] Darveaux J, Busse WW. Journal of Allergy and Clinical Immunology. 2015;3(2): 152-160.

[7] Bieber T, Cork M, Reitamo S. Atopic dermatitis: a candidate for disease-modifying strategy. Department of Dermatology and Allery 2012;67: 969-975.

[8] Thomson SF. Epidemiology and natural history of atopic diseases. European Clinical Respiratory Journal. 2015 Mar 24;2.

[9] American Journal of Respiratory and Critical Care Medicine. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide. 2005;171:912-930.

[10] M.R Miller, J.Hankison, V.Brusasco, F.Burgos, R.Casaburu, A. coates, et al. Series "ATS/ERS Task Force: Standardization of Lung Function Testing. 2005;26:319-338.

13.0 APPENDIX I: ASTHMA CONTROL QUESTIONNAIRE

Asthma Control Questionnaire **Patient ID:**

Date:

Page 1 of 2

Please answer questions 1-6

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

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

Asthma Control Questionnaire

Patient ID:

Date:

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

To be completed by a member of the clinic staff

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

FEV_1 = forced expiratory volume in 1 second

14.0 APPENDIX II: PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Since beginning of treatment (Day 1) in this study, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your asthma? (Please tick ONE box).

1 = Very much improved ❑

2 = Much improved ❑

3 = Minimally improved ❑

4 = No changes ❑

5 = Minimally worse ❑

6 = Much worse ❑

7 = Very much worse ❑

15.0 APPENDIX III: CLINICAL GLOBAL IMPRESSION OF CHANGE (CGIC) SCALE

Since this patient has started the study treatment (Day 1) how would you describe the change (if any) in this patient's overall asthma symptoms and control compared to their asthma on Day 1. Please tick ONE box.

1 = Very much improved ❑

2 = Much improved ❑

3 = Minimally improved ❑

4 = No changes ❑

5 = Minimally worse ❑

6 = Much worse ❑

7 = Very much worse ❑

16.0 APPENDIX IV: GLOBAL INITIATIVE FOR ASTHMA (2016) ASSESSMENT OF SEVERITY AND STEP THERAPY

Assessing Asthma Severity

Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It can be assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years.

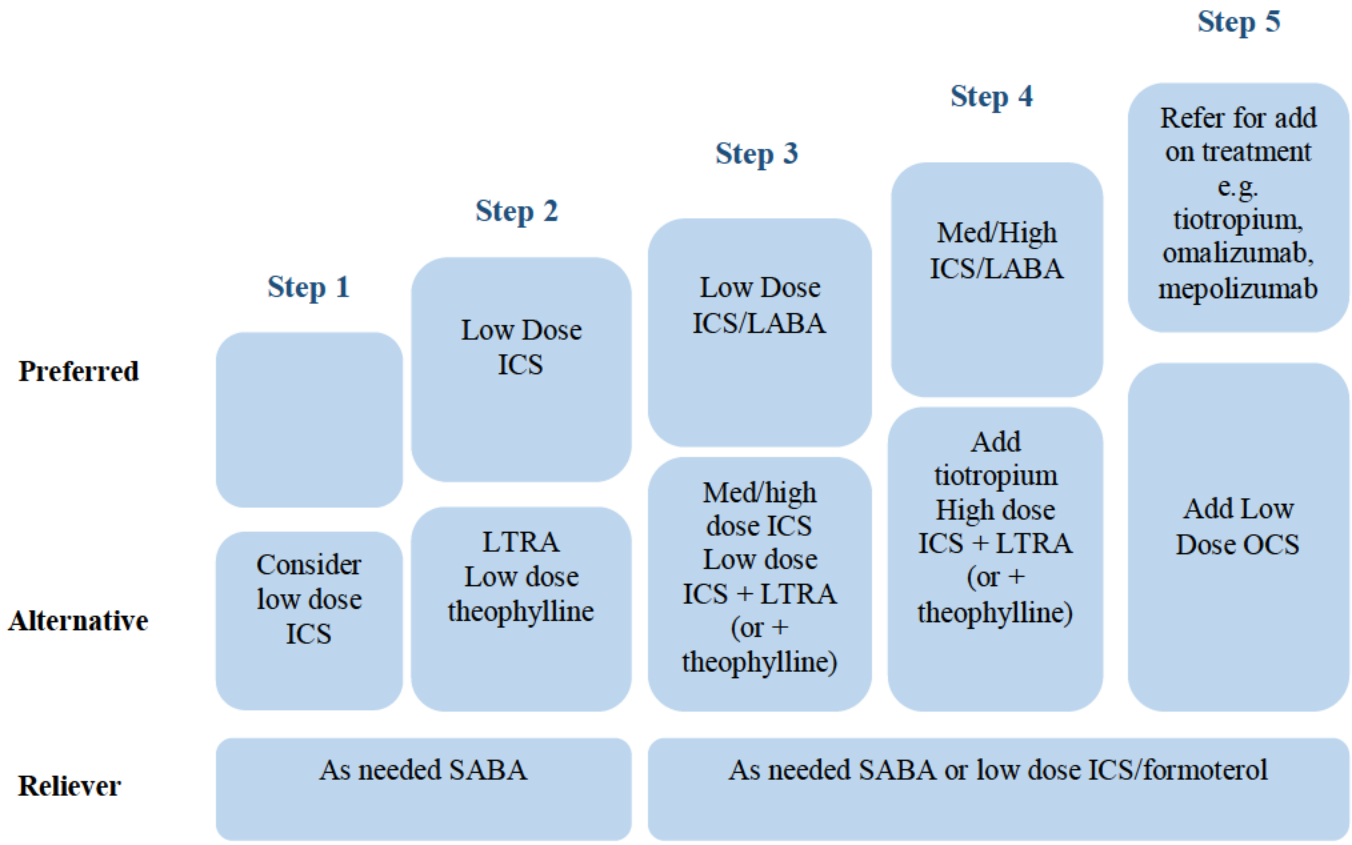
Asthma severity can be assessed when the patient has been on regular controller treatment for several months:

Mild asthma is asthma that is well controlled with Step 1 or Step 2 treatment, i.e. with as needed reliever medication alone, or with low-intensity controller treatment such as low dose inhaled corticosteroids (ICS), leukotriene receptor antagonists, or chromones.

Moderate asthma is asthma that is well controlled with Step 3 treatment e.g. low dose ICS/long-acting beta-2-agonists (LABA).

Severe asthma is asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.

Step Therapy



Abbreviations: ICS = inhaled corticosteroids; LABA = long-acting beta-2-agonists; LTRA = leukotriene receptor antagonists; Med = medium; OCS = oral corticosteroids; SABA = short-acting beta agonists.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available from: www.ginasthma.org

17.0 APPENDIX V: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: Placebo-Controlled Proof of Concept Study to Investigate ANB020 Activity in Adult Patients with Severe Eosinophilic Asthma

PROTOCOL NO: ANB020-004

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 IQVIA.

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: _____

_____

_____

18.0 APPENDIX VI: PHARMACOKINETIC, INTERFERON-GAMMA, ANTI-DRUG ANTIBODY, AND BIOMARKER CYTOKINES COLLECTION TIME POINTS

Study Visit	Pharmacokinetic Sample Time Point (Serum)	Sample Time Point for ex vivo induced IFN-γ	Sample Time Point for ADA	Pharmacodynamic Sample Time point for Cytokines (Serum)
Day 1 ANB020/ Placebo Dosing	Pre-dose (≥5 minutes) 0.50 hours (±5 minutes) post-start of infusion EOI (+≤3 minutes) EOI+3 hours (±10 minutes) EOI+6 hours (±10 minutes	Pre-dose (≥5 minutes)	Pre-dose (≥5 minutes)	Pre-dose (≥5 minutes)
Day 2	24 hours (±120 minutes) post-start of infusion			24 hours (±120 minutes) post-start of infusion
Day 8	168 hours (±120 minutes) post-start of infusion		168 hours (±120 minutes) post-start of infusion	168 hours (±120 minutes) post-start of infusion
Day 22	504 hours (±120 minutes) post-start of infusion			504 hours (±120 minutes) post-start of infusion
Day 36	840 hours (±120 minutes) post-start of infusion		840 hours (±120 minutes) post-start of infusion	840 hours (±120 minutes) post-start of infusion
Day 64	1512 hours (±120 minutes) post-start of infusion			1512 hours (±120 minutes) post-start of infusion
Day 85			2016 hours (±120 minutes) post-start of infusion	
Day 106			2520 hours (±120 minutes) post-start of infusion	

Study Visit	Pharmacokinetic Sample Time Point (Serum)	Sample Time Point for ex vivo induced IFN-γ	Sample Time Point for ADA	Pharmacodynamic Sample Time point for Cytokines (Serum)
Day 127 EOS/ ET[a]		3024 hours (±120 minutes) post-start of infusion	3024 hours (±120 minutes) post-start of infusion	3024 hours (±120 minutes) post-start of infusion

Abbreviation: ADA = anti-drug antibody, EOI = actual time of end of infusion, EOS = End of study, ET = early termination, IFN-γ = interferon-gamma.
Time point details may shift beginning Day 36 depending on use of +/- 2-day window.

a If the patient discontinues from study before Day 127 and returns to site for early termination (ET) visit, the samples for IFN-γ, ADA, and cytokines will be collected at ET visit. A sample for PK analysis will also be collected if the ET visit occurs between Day 1 to Day 64. Duplicate samples will not be collected if the sample at ET visit would fall within another specified sample time/window.

19.0 APPENDIX 7: SUMMARY OF CHANGES

Protocol ANB020-004: Amendment 3, 16 February, 2018

Replaces: Amendment 2, 04 January, 2018

1. Inclusion Criteria Updated:
   Description of Change: Lowered required blood eosinophil count from ≥400 to ≥300 cells/µL.
   Purpose for Change: To enable enrollment of severe eosinophilic patients with levels of ≥300 cells/µL.

2. Section 5.4 (Method of Assigning Patients to Treatment Group):
   Description of Change: Removed specific details on randomization responsibilities.
   Purpose for Change: Instructed site to reference study manuals for complete information/instruction.

3. Section 5.7.2 (Unblinding):
   Description of Change: Removed specific details on unblinding language.
   Purpose for Change: Site staff to reference study manuals for detailed processes.

Protocol ANB020-004: Amendment 2, 04 January, 2018

Replaces: Amendment 1, 08 May 2017

1. Entire Document:
   a. Description of Change: Updated CRO name from QuintilesIMS to IQVIA.
      Purpose for Change: Vendor name change.

   b. Description of Change: General grammatical and typographical corrections.
      Purpose for Change: Correcting errors.

2. Synopsis- Study Center:
   Description of Change: Updated number of study centers.
   Purpose for Change: Increase number of sites participating in protocol.

3. Section 2.1- (Background Information) and Section 4.2 (Discussion of Study Design):
   Description of Change: Updated background to include MAD information.
   Purpose for Change: Updated to reflect completion of MAD study as reflected in current IB.

4. Section 4.1 (Summary of Study Design):
   Description of Change: Clarification of informed consent window.
   Purpose for Change: Remove "-14-day" window restriction to allow consent prior to screening visit.

5. Section 4.3.1 (Inclusion Criteria):
   a. Description of Change: Increased body mass index.
      Purpose for Change: Increased to reflect BMI of patient population.

   b. Description of Change: Clarified WOCBP language.
      Purpose for Change: Clarified to address Investigator questions.

   c. Description of Change: Inclusion Systemic corticosteroids dosage criteria, removal of stable dose requirement.
      Purpose for Change: Removed stable dosage requirement to correspond with SOC treatment prior to beginning study treatment.

6. Section 4.3.2 (Exclusion Criteria)
   a. Description of Change: Removed exclusion: "Participation in any interventional study for the treatment of asthma in the 6 months before screening."
      Purpose for Change: Removed, covered in exclusion criteria "3 months or 5 half-lives before screening."

   b. Description of Change: Removed exclusion for use of beta blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or calcium channel blockers.
      Purpose for Change: Use of beta blockers, etc. will not affect safety of participants and will allow SOC treatment to continue.

   c. Description of Change: Inclusion amended to allow admission of controlled cardiovascular disease (controlled ischemic cardiovascular disease).

Purpose for Change: Allow inclusion of typical patient population.

7. Section 4.3.4 (Patient Restrictions):
   Description of Change: Clarified language regarding partners of male patients and clarified "Highly Effective Methods of Contraception" language to reflect local naming conventions.
   Purpose for Change: Clarified requirements for contraception.

8. Section 4.3.5 (Patient Withdrawal):
   Description of Change: Added notification instructions for staff.
   Purpose for Change: Provide instruction to site regarding notification procedures.

9. Section 5.8.1 (Excluded Medications):
   Description of Change: Removed restricted medications per inclusion/exclusion updates.
   Purpose for Change: Updates correspond to revised inclusion/exclusion criteria.

10. Section 6.1.2 (Spirometry):
    Description of Change: Addition of pre-bronchodilator Spirometry readings at each clinic visit.
    Purpose for Change: Additional Spirometry reading collected to ensure stable collection of data.

11. Section 6.2.6 (Timing of Procedures):
    a. Description of Change: Corrected order of blood draw.
       Purpose for Change: Updated to reflect laboratory instruction guidelines.

    b. Description of Change: Removed repetitive Quality of Life instruction.
       Purpose for Change: Removed repetitive instruction that is covered in bullet point #3 (study scales/questionnaire forms).

12. Section18 (Appendix VI - IFN-γ collection time points):
    Description of Change: Removed select IFN-γ blood draws.
    Purpose for Change: Additional blood draws unnecessary per data collected in previous trials.

13. Table 4.1 (Schedule of Events):
    Description of Change: Corrected footnotes to reflect Amendment 2 changes.
    Purpose for Change: Updated to reflect necessary changes in procedure requirements.

Protocol ANB020-004: Amendment 1, 08 May 2017

Replaces: Original: 21 Mar 2017

1. Section 4.3.1 (Inclusion Criteria)
   Description of Change: Corrected length of time contraception is required following last dose of IP administration from 20 weeks to 18 weeks for both male and female participants.
   Purpose for Change: Corrected length of time to 18 weeks to accurately reflect 5 half-lives of ANB020 300mg IV plus an additional 50 days for sperm turnover.

2. Section 4.3.4 (Patient Restrictions)
   a. Description of Change: Corrected length of time contraception is required following last dose from 20 weeks to 18 weeks for both male and female patients.
      Purpose for Change: Typographical error, length of time was decreased based on half-life of ANB020.
   b. Description of Change: Corrected five times half-life of drug from 85 days to 70 days.
      Purpose for Change: To provide accurate ANB020 half-life information based on 300mg IV dosing of ANB020.

3. Section 5.7 (Blinding)
   Description of Change: Updated headings in section 5.7 to include unblinding information and provide details for unblinding procedures.
   Purpose for Change: To provide unblinding information and instruction should unblinding be necessary during the study.