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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING STUDY INVESTIGATING THE EFFICACY, SAFETY, AND PHARMACOKINETIC PROFILES OF REGN3500 ADMINISTERED TO ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Compound:	REGN3500
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AMENDMENT HISTORY

Amendment 3

This amendment incorporates recommendations from a European clinical trial review and corrections to a number of inconsistencies. The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Changes based on recommendation from the European clinical trial review:	
Added secondary safety and pharmacokinetic (PK) endpoints.	Synopsis, Secondary Endpoints, Statistical Plan Section 4.2.2 Secondary Endpoints Section 10.1 Statistical Hypothesis
Added study stopping rules	Section 5.1.1 Study Stopping Rules (added) Section 5.1.2 End of Study Definition (section number changed, no content change) Section 5.3.1 Independent Data Monitoring Committee
Administrative changes to correct inconsistencies:	
In Amendment 2, Inclusion Criterion #1 was revised to add an upper age limit of 75 years. This change was not incorporated in the Target Population section of the Synopsis and is incorporated in Amendment 3.	Synopsis, Target Population
In Amendment 2, text was added in Exclusion Criterion #12 to specify that patients with a positive tuberculosis (TB) QuantiFERON test result will be excluded from the study. This change was not incorporated in Section 8.2.1 and Section 8.2.3.5 and is incorporated in these sections in Amendment 3. This change was incorporated in Table 2 in Amendment 2, but not listed in "Section Changed", and is now added.	Amendment History, Amendment 2 Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.3.5 Laboratory Testing

Amendment 2

This amendment incorporates recommendations from the European Union clinical trial review. The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Revised the text regarding onsite monitoring after each administration of study drug to indicate that the minimum 30 minutes monitoring may be extended to up to 2 hours as per country-specific requirements.	Synopsis Study Design Section 5.1 Study Description and Duration Section 7.1 Investigational and Reference Treatments Section 8.1.1 Footnotes for the Schedule of Events Table, #3
Revised Inclusion Criterion #1 to add an upper age limit of 75 years.	Section 6.2 Study Population Section 6.2.1 Inclusion Criteria, #1

Change and Rationale for Change	Section Changed
Added text in Exclusion Criterion #12 to specify that patients with a positive tuberculosis (TB) QuantiFERON test result will be excluded from the study.	Table 2 Schedule of Events Section 6.2.2 Exclusion Criteria, # 12 Section 8.1.1 Footnotes for the Schedule of Events Table, #9
Exclusion Criterion # 20: Added myocardial infarction, unstable arterial hypertension, unstable angina, and cerebrovascular accident as examples of uncontrolled cerebrocardiovascular conditions that will exclude a patient from the study.	Section 6.2.2 Exclusion Criteria, # 20
Exclusion Criterion #25: Added clarification that the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient, based on Clinical Trial Facilitation Group guideline on contraception.	Section 6.2.2 Exclusion Criteria, # 25
Added note in Table 1 Dosing Regimen and added text in Footnote #3 for the Schedule of Events Table to clarify that in order to maintain blinding, all patients will receive every 2 weeks (Q2W) subcutaneous (SC) injections. For the REGN3500 300 mg SC every 4 weeks (Q4W) group, REGN3500 100 mg SC Q4W group, and REGN3500 30 mg SC every 8 weeks (Q8W) group, there will be SC injection(s) of placebo in between REGN3500 doses so the injection frequency will match the other 2 groups (REGN3500 Q2W and placebo Q2W).	Section 7.1 Investigational and Reference Treatments, Table 1 Section 8.1.1 Footnotes for the Schedule of Events Table, #3
Changed the neutrophil count criterion for permanent discontinuation of study drug from $\leq 0.5\times10^3/\mu L$ to $\leq 1.0\times10^3/\mu L$ and for temporary discontinuation of study drug from $\leq 1.0\times10^3/\mu L$ but $>0.5\times10^3/\mu L$ to $\leq 1.5\times10^3/\mu L$ but $>1.0\times10^3/\mu L$.	Section 7.4.2.1 Reasons for Permanent Discontinuation of Study Drug Section 7.4.2.2 Reasons for Temporary Discontinuation of Study Drug

Amendment 1

The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Modified exclusion criterion #4 to decrease the length of the washout period from 12 weeks to 4 weeks before the baseline visit for immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon-gamma [IFN-γ], Janus kinase inhibitors, azathioprine, methotrexate, etc) and phototherapy. These washout changes are consistent with the prior dupilumab adult atopic dermatitis phase 3 studies (eg, R668-AD-1224) and should be acceptable for patients enrolled in this study.	Section 6.2.2 Exclusion Criteria, #4
Removed statements that oral antibiotic use ≤7 days was considered rescue treatment for atopic dermatitis (AD). Patients are allowed to receive oral antibiotics for up to 14 days per course to treat infections and this is not considered rescue treatment for AD. This change is consistent with prior dupilumab adult atopic dermatitis phase 3 studies (eg, R668-AD-1224).	Synopsis, Treatments Section 7.3 Rescue Treatment Section 7.4.2.1 Reasons for Permanent Discontinuation of Study Drug Section 7.4.2.2 Reasons for Temporary Discontinuation of Study Drug Section 7.7.2 Permitted Medications and Procedures Section 7.7.2.1 Prohibited Concomitant Medications or Procedures as Rescue Treatment
Removed mandatory ophthalmological eye exams. Instead, limit an ophthalmological exam during screening to those patients who have history of certain eye disorders (conjunctivitis, blepharitis, or keratitis) within the last 12 months and, after randomization, to patients who experience adverse events of special interest (AESIs) related to eye disorders. This change is to reduce patient burden yet allow a robust and comprehensive evaluation of baseline disease status of patients with history of these disorders, as well as of any treatment-emergent adverse events (TEAEs) falling under this category. These ophthalmologic exam changes are consistent with the dupilumab pediatric phase 3 study R668-AD-1652.	Table 2 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #8, #17 Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.3.7 Ophthalmologic (Eye) Examinations Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Updated exclusion criterion #11 to be consistent with prior dupilumab adult atopic dermatitis phase 3 studies (eg, R668-AD-1224). Active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks (was previously 8 weeks before the screening visit) before the baseline visit, or superficial skin infections within 1 week (was previously 4 weeks before the screening visit) before the baseline visit. NOTE: patients may be rescreened after the infection resolves.	Section 6.2.2 Exclusion Criteria, #11
As recommended from the FDA for Protocol R3500-AD-1798, added urine pregnancy tests at week 20 and week 28.	Table 2 Schedule of Events
Removed hematology and chemistry from visit 3, visit 5, visit 7, and visit 9 to reduce the patient burden of blood draws.	Table 2 Schedule of Events

Change and Rationale for Change	Section Changed
To address FDA comments, Footnote #20 added to state that in the event a patient sample is positive in the REGN3500 ADA assay at Week 16 or the first time point analyzed, the Week 4 PK sample may be analyzed in the ADA assay.	Table 2 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #20
Minor editorial changes	Table 2 Schedule of Events

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Investigating the Efficacy, Safety, and Pharmacokinetic Profiles of REGN3500 Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
Site Locations	Approximately 100 multinational study sites
Objectives	The primary objective of the study is to assess the efficacy of REGN3500 monotherapy in atopic dermatitis (AD), as well as understand the dose-response relationship, compared with placebo treatment, in adult patients with moderate-to-severe AD. The secondary objectives of the study are: • To assess the safety and tolerability of subcutaneous (SC) doses of REGN3500 monotherapy in adult patients with moderate-to-severe AD • To assess the pharmacokinetics (PK) of REGN3500 in adult patients with moderate-to-severe AD • To assess the immunogenicity of REGN3500 in adult patients with moderate-to-severe AD The exploratory objectives of the study are to assess the effects of REGN3500 monotherapy on skin and blood biomarkers of inflammation, quality-of-life (QOL), and patient-reported measures of pain and sleep quality in comparison with placebo.
Study Design	This is a randomized, double-blind, placebo-controlled, double-dummy, parallel-group study to assess the dose-response profile of various REGN3500 monotherapy dosing regimens in adult patients with moderate-to-severe AD. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. After providing informed consent, patients will be assessed for study eligibility at a screening visit (within 5 weeks [ie, 35 days] prior to randomization). During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, medication use, concomitant illness, medical condition), unless the reason for the screen failure is related to failing the disease severity inclusion criteria.

	Patients will be required to apply moisturizers (bland emollients) at least twice daily for at least 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be eighth day) and throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on any area(s) of lesional or non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. Patients who meet eligibility criteria during the screening period will undergo day 1/baseline assessments. Patients who continue to meet eligibility criteria at baseline will be randomized in a 1:1:1:1:1 ratio to receive 1 of 5 treatment regimens (4 active, 1 placebo) for a 16-week double-blind treatment period followed by a 20-week post-treatment follow up. Randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (IGA=3)] vs. severe [IGA=4] AD). It is planned that at least approximately 50% of patients randomized will have an IGA score of 4. To ensure enrollment according to intended distribution of disease severity, alerts will be built into the interactive voice/web response system to limit enrolling patients with an IGA score <4. Patients will remain at the study site for a minimum of 30 minutes after administration of study drug, and the monitoring period may be extended up to 2 hours as per country-specific requirements. During the 16-week treatment period, patients will have study visits every other week. If medically necessary (ie, to control intolerable AD symptoms), patients may receive rescue treatment (eg, systemic and topical corticosteroids) at the discretion of the investigator. The end-of-treatment visit will occur at week 16, which is 2 weeks after the last dose of study drug. The primary endpoint will be evaluated at week 16. The duration of the 20-week post-treatment follow-up period corresponds to approximately 5 half-lives of REGN3500 (half-life ~30 days). The end-of-study visit will occur at week 36.
Study Duration	Each patient's participation in the study will be up to 41 weeks, including an up to 5-week (ie, 35 days) screening period, 16-week double-blind treatment period, and 20-week post-treatment follow-up period.
End of Study Definition	The end of the study for this study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 300 patients will be randomized (60 per treatment group).
Target Population:	Male or female adult patients (≥18 to 75 years of age) with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatments are medically inadvisable (eg, intolerance, other important side effects or safety risks).

Treatment(s)

Study Drug	REGN3500 is supplied in vials as a lyophilized powder for reconstitution and SC administration.
Dose/Route/Schedule:	REGN3500 SC: 300 mg SC every 2 weeks (Q2W), 300 mg SC every 4 weeks (Q4W), 100 mg SC Q4W, or 30 mg SC every 8 weeks (Q8W) from day 1 through week 14
Placebo	Placebo that matches REGN3500 (REGN3500-matching placebo) will be prepared in the same formulation as REGN3500, without the addition of protein, for SC administration.
Route/Schedule:	REGN3500-matching placebo SC administration schedule is driven by the treatment assignment to achieve blinding across treatment groups.
Treatment Regimens:	**REGN3500 300 mg SC Q2W**: 2 injections of REGN3500 (300 mg total dose) plus 1 injection of REGN3500-matching placebo administered SC on day 1 and week 8; and 2 injections of REGN3500 (300 mg total dose) administered SC at weeks 2, 4, 6, 10, 12, and 14. **REGN3500 300 mg SC Q4W**: 2 injections of REGN3500 (300 mg total dose) plus 1 injection of REGN3500-matching placebo administered SC on day 1 and week 8; 2 injections of REGN3500 (300 mg total dose) administered SC at weeks 4 and 12; and 2 injections of REGN3500-matching placebo administered SC at weeks 2, 6, 10, and 14. **REGN3500 100 mg SC Q4W**: 1 injection of REGN3500 (100 mg total dose) plus 2 injections of REGN3500-matching placebo administered SC on day 1 and week 8; 1 injection of REGN3500 (100 mg total dose) plus 1 injection of REGN3500-matching placebo administered SC at weeks 4 and 12; and 2 injections of REGN3500-matching placebo administered SC at weeks 2, 6, 10, and 14. **REGN3500 30 mg SC Q8W**: 1 injection of REGN3500 (30 mg total dose) plus 2 injections of REGN3500-matching placebo administered SC on day 1 and week 8; and 2 injections of REGN3500-matching placebo administered SC at weeks 2, 4, 6, 10, 12, and 14. **Placebo SC Q2W**: 3 injections of REGN3500-matching placebo on day 1 and week 8; and 2 injections of REGN3500-matching placebo administered SC at weeks 2, 4, 6, 10, 12, and 14.
Background Treatment:	All patients must apply moisturizers (bland emollients) at least twice daily for at least 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be the eighth day) and throughout study participation. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on any area(s) of lesional or non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Rescue Treatment:	If medically necessary (ie, to control intolerable AD symptoms), patients may receive rescue treatment for AD at the discretion of the investigator. If rescue treatment consists of topical medications (eg, topical corticosteroids, topical calcineurin inhibitors, or topical crisaborole) the patient can continue study treatment. If rescue treatment consists of systemic corticosteroids or non-steroidal systemic immunosuppressive drugs, study treatment will be permanently discontinued immediately.

Endpoint(s)

Primary: The primary endpoint in the study is the percent change in Eczema Area and Severity Index (EASI) score from baseline to week 16.

Secondary: The secondary endpoints are:

Efficacy:

- Proportion of patients achieving EASI-50, EASI-75, and EASI-90 (≥50%, ≥75%, and ≥90% improvement from baseline) at week 16
- Absolute change in EASI scores from baseline to week 16
- Proportion of patients with both an IGA score of 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
- Change (absolute and percent) from baseline to week 16 in weekly average of daily peak Pruritus Numerical Rating Scale (NRS)
- Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline at week 16
- Time to onset of effect on pruritus during the 16-week treatment period (≥4-point reduction of weekly average of daily peak Pruritus NRS from baseline)
- Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
- Change from baseline to week 16 in percent Body Surface Area (BSA) of AD involvement

Safety:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through end of treatment (week 16)
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through end of treatment (week 16)
- Incidence of treatment-emergent adverse events of special interest (AESIs) from baseline through end of treatment (week 16)
- Incidence of TEAEs from baseline through end of study (week 36)
- Incidence of treatment-emergent SAEs from baseline through end of study (week 36)

	• Incidence of treatment-emergent AESIs from baseline through end of study (week 36) **Pharmacokinetic (PK):** • Concentrations of functional REGN3500 in serum by treatment regimen at each assessment time point from baseline to end of study (week 36) Note: The safety and PK endpoints will not be included in the testing hierarchy.
Procedures and Assessments	A variety of parameters will be collected during the study to assess the efficacy, including various measures of AD severity (EASI, SCORAD, IGA, Pruritus NRS, Pain NRS, Sleep Quality NRS, Global Individual Signs Score, and BSA) and patient reported measures of AD symptoms and QOL (Dermatology Life Quality Index [DLQI], Patient Orientated Eczema Measure [POEM], and Hospital Anxiety and Depression Scale [HADS]). Safety and tolerability will be monitored by clinical assessment of adverse events (AEs) and by repeated measurements of clinical evaluation including vital signs (body temperature and sitting blood pressure, pulse, and respiration rate), physical examinations, eye examinations 12-lead electrocardiograms (ECGs), and laboratory assessment including standard hematology, chemistry, and urinalysis. Blood samples for the determination of functional REGN3500 and anti-drug antibody (ADA) in serum will be collected. Serum and plasma samples will be collected for analysis of additional biomarkers, including total interleukin-33 (IL-33), thymus and activation-regulated chemokine (CCL17; TARC), total immunoglobulin E (IgE), high-sensitivity C-reactive protein (hs-CRP), and serum amyloid A (SAA). Whole blood samples will also be collected for DNA and RNA extraction and pharmacogenomics evaluation. Plasma and serum will be banked for future biomedical research.
Statistical Plan	For the primary endpoint, the enrollment of 60 patients per treatment group will provide 96% power to detect a 35% difference between the most efficacious REGN3500 SC dose and the placebo group with respect to percent change in EASI score from baseline to week 16, assuming the common standard deviation (SD) is 50%, with a 2-sided test at the 0.05 significance level. The 50% SD along with the 35% difference in the mean percent were estimated based on results from 2 phase 3 dupilumab AD studies (R668-AD-1334 and R668-AD-1416). The efficacy endpoints will be analyzed using the full analysis set (FAS) which includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized). To control the overall family-wise type I error rate of 5%, a hierarchical procedure from high to low dose will be performed for the primary endpoint and selected secondary efficacy endpoints (eg, EASI-75, IGA score of 0 or 1 and a reduction from baseline of

≥2 points responder at week 16) across the REGN3500 dose regimens versus placebo.

Continuous endpoints will be analyzed using an analysis of covariance (ANCOVA) model, which includes treatment group, stratification variable (moderate [IGA=3] vs. severe [IGA=4] AD) and relevant baseline value as covariates. The efficacy data will be set to missing after rescue treatment is used, then all missing data from the FAS will be imputed 40 times under missing at random assumption to generate a complete dataset at each imputation by using the multiple imputation (MI) Statistical Analysis System (SAS) procedure. These complete datasets will be analyzed using an ANCOVA model and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula. Sensitivity analyses such as ANCOVA model with last observation carried forward, MI method with ANCOVA model on all observed data regardless of rescue treatment use will be conducted. Categorical endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline disease severity stratum. Patients will be considered as non-responders at the time point where data are missing (regardless of reason for missingness, eg, due to drop-out or data set to missing after rescue treatment).

Safety analyses will be based on the safety analysis set (SAF), which includes all randomized patients who received any study drug. Reported TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and 12-lead ECG results) will be summarized by treatment group.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BSA	Body surface area (of involvement of atopic dermatitis)
C_{min}	Minimum concentration
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
EASI-50	≥50% improvement in EASI score
EASI-75	≥75% improvement in EASI score
EASI-90	≥90% improvement in EASI score
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
e-diary	electronic patient diary
EOS	End-of-study
EOT	End-of-treatment
ET	Early termination
FAS	Full analysis set
FBR	Future Biomedical Research
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GISS	Global Individual Signs Score

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

GWA	Genome wide association
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCV Ab	Hepatitis C virus antibody
HDM	House dust mite extract
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL1RL1	Interleukin-1 receptor-like 1
IL-4Rα	Interleukin-4 receptor alpha
ILC2	Type 2 innate lymphoid cells
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MI	Multiple imputation
NRS	Numerical Rating Scale
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
POC	Proof-of-concept
POEM	Patient Oriented Eczema Measure
PT	Preferred term

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Q1	First quartile
Q2W	Every 2 weeks
Q3	Third quartile
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QOL	Quality of life
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAA	Serum amyloid A
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TARC	Thymus and activation-regulated chemokine (CCL17)
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
WBC	White blood cell
WOCBP	Women of childbearing potential

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis, asthma, and food allergy. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber, 2008). The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics, and skin barrier dysfunction. Both the disturbances in epidermal barrier function and hyperactive immune response are associated with changes in the skin microbiome. Flares of AD are associated with an expansion of *Staphylococcus aureus* on lesional skin and a substantial loss of biodiversity in skin microbiome (Williams, 2017).

Skin-infiltrating leukocytes are thought to play a pivotal role in the initiation and amplification of atopic inflammation. The key cells involved in the pathophysiologic mechanism of AD are classified into 4 general subgroups. First, dendritic cell subtypes including Langerhans cells and inflammatory dendritic epithelial cells polarize T-helper cells via Immunoglobulin E (IgE) – and non-IgE-mediated mechanisms. Dendritic cells in the skin present allergens to lymphocytes, causing a Type 2 helper T cell (Th2) polarization and subsequent release of pro-inflammatory cytokines, which include interleukin (IL)-4, IL-5, and IL-13. The T-helper cells are the second group of cells. In acute exudative skin lesions, CCR4+ (chemokine 'C' receptor) Th2 cells are abundant and secrete cytokines IL-4, IL-13, and IL-5, whereas Type 1 helper T cells (Th1), which secrete interferon-gamma (IFN-γ), are also seen in chronic, lichenified lesions. Activated eosinophils are the third group of cells, causing local inflammation at lesional sites. Keratinocytes are the fourth cell-type involved in the pathophysiology of AD. These skin cells express high levels of the Th2 polarizing cytokine and thymic stromal lymphopoietin in AD lesions, which may amplify and sustain the allergic response (Suarez-Farinas, 2013). For patients with moderate-to-severe AD, topical therapies have limited efficacy, and systemic treatments are associated with substantial toxic effects. Dupilumab, a human monoclonal antibody (mAb) directed against the IL-4 receptor alpha (IL-4Rα) subunit, blocks IL-4 and IL-13 signaling. Dupilumab has been shown to be safe and efficacious and, as of March 2018, has been approved in the United States, European Union, and Japan, as well as in other countries, for treatment of adults with moderate-to-severe AD.

Interleukin-33 is a proinflammatory cytokine that initiates and amplifies innate and adaptive inflammatory cascades (Cayrol, 2014). Interleukin-33 is released by damaged epithelial tissue cells in response to insults such as allergens, viruses, or smoke. Interleukin-33 signaling activates multiple downstream inflammatory pathways, resulting in effects characteristic of both Type 1 and Type 2 inflammation. Genetic and experimental evidence suggest a role for IL-33 in pathogenesis of AD. Transgenic mice overexpressing IL-33 in the skin epithelium develop spontaneous AD-like symptoms associated with pruritus and immune cell infiltration (Imai, 2013). Experimentally-induced AD in mice results in IL-33-dependent infiltration of Type 2 innate lymphoid cells (ILC2), which are the source of Type 2 inflammatory cytokines (Salimi, 2013), however, this result appears to be strain dependent (Kim, 2013). Human genetic data (Hirota, 2012) (Paternoster, 2015) (Bonnelykke, 2013) (Shimizu, 2005) suggest that variants in the IL-33 pathways confer

susceptibility to AD. Data from AD patients suggest that IL-33 and IL1RL1 (interleukin-1 receptor-like 1 [the IL-33 receptor]) are upregulated in lesional skin (Savinko, 2012) (Salimi, 2013). Taken together, these data suggests that blockade of IL-33 may be efficacious in targeting inflammatory pathways active in AD.

Recently, publicly available results disclosed from an uncontrolled phase 2a study evaluating a single intravenous (IV) dose of an anti-IL-33 mAb (ANB020, AnaptysBio) in 12 moderate-to-severe adult AD patients offer mechanistic support for anti-IL-33 approach to improving AD disease severity (Ogg, 2018). In this proof-of-concept (POC) study, 83% of patients were reported to have achieved a ≥50% improvement in Eczema Area and Severity Index (EASI) score (EASI-50) at day 29 and an average EASI reduction of 62% by day 57 following dosing. Pruritus, as measured by 5-D Pruritus Scale score, was reduced by 21% at day 57.

REGN3500 (also referred to as SAR440340) is a human $IgG4^P$ mAb that binds IL-33 with subnanomolar affinity. REGN3500 has been studied in 3 phase 1 clinical studies evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) effects of REGN3500 in healthy volunteers and in patients with asthma.

In summary, genetic and experimental data, preclinical studies, and human clinical studies support further evaluation of REGN3500 in patients with moderate-to-severe AD. Additional background information on the study drug and development program can be found in the REGN3500 Investigator's Brochure.

The current study is proposed to assess the efficacy of multiple REGN3500 dose regimens, compared with placebo, in adult patients with moderate-to-severe AD who are intolerant of, or who are not adequately controlled with, topical treatments.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the efficacy of REGN3500 monotherapy in AD, as well as understand the dose-response relationship, compared with placebo treatment, in adult patients with moderate-to-severe AD.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of subcutaneous (SC) doses of REGN3500 monotherapy in adult patients with moderate-to-severe AD
- To assess the PK of REGN3500 in adult patients with moderate-to-severe AD

  To assess the immunogenicity of REGN3500 in adult patients with moderate-to-severe AD

2.3. Exploratory Objectives

The exploratory objectives of the study are to assess the effects of REGN3500 monotherapy on skin and blood biomarkers of inflammation, QOL, and patient-reported measures of pain and sleep quality in comparison with placebo.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Based on the mechanism of action of REGN3500, inhibition of IL-33, REGN3500 is expected to be efficacious in treatment of AD. This hypothesis will be tested by analysis of the changes from baseline in objective and subjective measures of skin inflammation, after treatment with different doses of REGN3500 or placebo to find an optimal dose regimen.

3.2. Rationale

3.2.1. Background

Dupilumab was approved as a safe and effective treatment for moderate-to-severe AD. Despite the significant clinical improvement provided by dupilumab in the majority of AD patients, there continues to exist an unmet medical need for additional therapies for AD.

Genetic and experimental evidence suggest a role for IL-33 in pathogenesis of AD. Transgenic mice overexpressing IL-33 in the skin epithelium develop spontaneous AD-like symptoms associated with pruritus and immune cell infiltration (Imai, 2013). Experimentally-induced AD in mice results in IL-33-dependent infiltration of ILC2 (Salimi, 2013), however this result appears to be strain dependent (Kim, 2013). In a separate experimental AD model, IL-33 signal transduction via the ST2-MyD88 pathway is pivotal for development of the AD phenotype (Li, 2017). Furthermore, an anti-IL-33 antibody has been shown to improve symptoms associated with AD in a mouse model of AD (Peng, 2018).

Large genome wide association (GWA) studies identified the IL1RL1 (ST2) locus as significantly associated with AD (Hirota, 2012) (Paternoster, 2015). Another recent GWA study identified a common 3 prime untranslated region (3' UTR) variant in IL1RL1 that was associated with allergic sensitization (Bonnelykke, 2013). Polymorphism in IL1RL1 correlates with an increased risk of AD (Shimizu, 2005).

In humans, IL-33 it is absent in normal human skin and induced by acute inflammation (Sundnes, 2015). Lesional AD skin expressed higher levels of IL1RL1 and IL-33 compared with healthy skin (Salimi, 2013) and non-lesional skin (Savinko, 2012). Interleukin-33 serum levels were reported to be higher in AD patients than in healthy controls or in urticaria or psoriasis patients (Tamagawa-Mineoka, 2014), however, assays may not accurately report circulating levels, and itch-induced tissue damage may cause release of IL-33 to circulation. Immune cells respond to IL-33 stimulation when IL-33 binds to its cognate receptor, ST2, and subsequently engages the co-receptor IL-1RAcP (interleukin-1 receptor accessory protein) to initiate signaling.

Preclinically, REGN3500 efficacy was evaluated in a 15-week model of allergen-induced lung inflammation using IL-33-humanized mice (REGN3500-MX-16008). Compared with unexposed *Il-33*$^{hu/hu}$ mice, mice exposed to house dust mite extract (HDM) for 15 weeks that were untreated or administered isotype control antibody showed significant increases in tissue remodeling and gross pathology (increased lung weight), lung eosinophil infiltration, lung tissue levels of MPO protein, a marker for neutrophilic tissue infiltration (Bradley, 1982), and Type 2 cytokines expression (IL-5 and IL-13). The HDM-exposed *Il-33*$^{hu/hu}$ mice administered REGN3500 after 4 weeks of HDM exposure had significantly reduced lung weights compared with untreated HDM-exposed mice and with HDM-exposed mice administered isotype control antibody. In this study, REGN3500 1 mg/kg SC dosed twice weekly was found to be the minimum efficacious dose for all endpoints evaluated, and an average serum concentration of 17 µg/mL (ie, 17 mg/L) was observed in mice in this dose group at the end of the study. REGN3500 blocked several pathologic markers of Type 1 and Type 2 immune responses in a 15-week HDM-induced lung inflammation in mouse model. Efficacy was associated with detectable concentrations of REGN3500.

REGN3500 has been studied in 3 phase 1 clinical studies evaluating the safety, tolerability, PK, and PD effects of REGN3500 in healthy volunteers and patients with asthma. To date, no serious adverse events (SAEs) have been reported in healthy adult subjects after single doses of REGN3500 up to 10 mg/kg IV in the first-in-human (FIH) study (R3500-HV-1551) or in asthmatic patients during the ongoing first-in-patient study after multiple doses of REGN3500 up to 150 mg SC (R3500-AS-1619). A phase 1 bronchial allergen challenge study (R3500-AS-1633), which has a cohort of REGN3500 (10 mg/kg IV on day 1) in combination with dupilumab (600 mg total loading dose on day 1 and 300 mg on day 15), is currently ongoing. In blinded data to date, no SAEs have been reported. In the phase 1 clinical studies, REGN3500 appears to have linear and dose-proportional PK with a half-life of approximately 30 days and no evidence of target mediated clearance, even at the lowest doses evaluated (0.3 mg/kg IV). The PK of REGN3500 appears to be similar between healthy volunteers and patients with asthma.

REGN3500 monotherapy and REGN3500 in combination with dupilumab are also being studied in a 12-week, phase 2a POC study (SAR440340-ACT15102) in adult patients with moderate-to-severe asthma who are not well controlled on inhaled corticosteroids plus long-acting beta 2 adrenergic agonist therapy. The SC doses of REGN3500 (300 mg) and dupilumab (300 mg) used in this POC study in asthmatic patients are the same as those to be used in the current POC study in AD patients. The POC study in asthmatic patients is currently ongoing, with the first patient enrolled in April 2018. In blinded data to date, no SAEs have been reported.

In addition to this phase 2b dose-ranging study in AD, clinical studies evaluating REGN3500 will include POC studies in patients with asthma, chronic obstructive pulmonary disease (COPD), and AD. These studies will evaluate monotherapy efficacy in addition to combination efficacy with dupilumab.

An anti-IL-33 mAb (ANB020, AnaptysBio) has also been evaluated in patients with moderate-to-severe AD. Publicly available results disclosed from an uncontrolled phase 2a study evaluating a single IV dose of an anti-IL-33 mAb (ANB020) in 12 moderate-to-severe adult AD patients offer mechanistic support for anti-IL-33 approach to improving AD disease severity (Ogg, 2018). In this study, 83% of patients were reported to have achieved EASI-50 at day 29 and an average EASI reduction of 62% by day 57 following dosing. Pruritus, as measured by 5-D Pruritus Scale score, was reduced by 21% at day 57. These results await confirmation in larger placebo-controlled phase 3 studies. Nevertheless, they may offer support for an anti-IL-33 approach to improving disease severity for patients with moderate-to-severe AD.

In summary, genetic and experimental data, preclinical studies, and human clinical studies support further evaluation of REGN3500 in patients with moderate-to-severe AD.

3.2.2. Rationale for Study Design

This is a phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study investigating the efficacy, safety, and PK profiles of REGN3500 administered to adult patients with moderate-to-severe AD over 16 weeks of treatment. This study is intended to provide information regarding 4 different REGN3500 monotherapy dosing regimens. Each REGN3500 dosing regimen will be compared with placebo to enable robust assessment of efficacy and safety.

The primary objective of this study is to assess the efficacy of REGN3500 monotherapy in AD, as well as understand the dose-response relationship, compared with placebo, in adult patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (side effects or safety risks). The primary objective of this study will be assessed using EASI scores. Secondary objectives are to assess the safety, tolerability, PK, and immunogenicity of REGN3500 monotherapy compared with placebo treatment in adult patients with moderate-to-severe AD.

Study treatment will be administered for 16 weeks and will constitute the double-blind, placebo-controlled treatment period. The 16-week treatment period is considered sufficient to assess treatment effect as measured by EASI, an endpoint allowing assessment of disease severity. A follow-up period of 20 weeks (approximately 5 half-lives of REGN3500) off study drug will enable appropriate assessment of safety and PK.

The choice of placebo as a control is appropriate for the objectives of this study as it will provide the most robust assessment of the efficacy and safety of REGN3500 monotherapy.

Additionally, for the primary endpoint, the enrollment of 60 patients per treatment group will provide 96% power to detect a 35% difference between the most efficacious REGN3500 SC dose and the placebo group with respect to percent change in EASI score from baseline to week 16.

The target population includes adults with moderate-to-severe AD who cannot be adequately controlled with topical medications or for whom topical treatment is otherwise inadvisable (eg, intolerance, other important side effects or safety risks). There remains an unmet need within this population for therapeutics intended to alleviate disease burden. Patients will be evaluated for chronic (at least 3 years) AD according to the American Academy of Dermatology Consensus Criteria and will be screened based on EASI and Investigator's Global Assessment (IGA) scores, as well as extent of body surface area (BSA) of AD involvement.

3.2.3. Rationale for Dose Selection

The dose regimens selected for this study are:

1. REGN3500 SC 300 mg every 2 weeks (Q2W) (high anchor, to be studied in phase 2a)
2. REGN3500 SC 300 mg every 4 weeks (Q4W)
3. REGN3500 SC 100 mg Q4W
4. REGN3500 SC 30 mg every 8 weeks (Q8W) (low anchor)
5. Placebo SC Q2W

The highest dosing regimen proposed for this study is 300 mg SC Q2W. The highest dose in the FIH single-ascending dose study (R3500-HV-1551) shown to have adequate safety was 10 mg/kg IV, which provides single-dose exposure and safety coverage for the 300 mg SC dose in this study. Safety after repeated dose administration of REGN3500 is supported by the results of the chronic safety study in cynomolgus monkeys where doses as high as 100 mg/kg were administered weekly SC for 26 weeks. Based on this no-observed-adverse-effect level and human exposure predictions from a standard linear 2-compartmental model, there is approximately a 30-fold exposure multiple for both maximum concentration at steady state and cumulative area under the curve for the highest regimen of 300 mg SC Q2W administered for 24 weeks. Thus, there are adequate safety data to support the selected dosing regimens in the current study administered over the treatment duration (16 weeks).

In addition to safety, PK-PD factors were considered. Based on results of an HDM-induced chronic lung inflammation mouse model, efficacy was observed at REGN3500 exposure levels of 1.5 mg/L (0.25 mg/kg) and 17 mg/L (1 mg/kg dose), although efficacy across multiple endpoints was demonstrated most consistently at 17 mg/L. Based on modeling of R3500-HV-1551 FIH drug concentrations, the regimens selected for the current study are expected (based on PK simulation) to achieve a range of minimum concentration (C_{min}) at steady state which brackets the 17 mg/L concentration threshold for efficacy identified in the HDM animal model. Specifically, the low anchor dosing regimen of REGN3500 30 mg SC Q8W regimen is expected to achieve a C_{min} at steady state (5 mg/L) which is close to the lower HDM efficacy threshold observed in the HDM animal model (1.5 mg/L). The high anchor dosing regimen of 300 mg SC Q2W is expected to achieve a C_{min} at steady state which is approximately 5-fold higher than the 17 mg/L concentration (higher HDM efficacy threshold). The higher exposure of the 300 mg SC Q2W regimen should conservatively ensure all patients are above the efficacy threshold when taking into account PK inter-individual variability, as well as the uncertainty in translating the PD of REGN3500 from the HDM mouse model to AD in humans.

Based on the above rationales, the 300 mg SC Q2W regimen of REGN3500 is currently being studied in other POC studies that are already underway (eg, SAR440340-ACT15102 [asthma], SAR440340-ACT15104 [COPD]).

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography, disease characteristics including medical history, and medication history for each patient.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint in the study is the percent change in EASI score from baseline to week 16.

4.2.2. Secondary Endpoints

The secondary endpoints are:

Efficacy:

- Proportion of patients achieving EASI-50, EASI-75, and EASI-90 (≥50%, ≥75%, and ≥90% improvement from baseline) at week 16
- Absolute change in EASI scores from baseline to week 16
- Proportion of patients with both an IGA score of 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16
- Change (absolute and percent) from baseline to week 16 in weekly average of daily peak Pruritus Numerical Rating Scale (NRS)
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16
- Time to onset of effect on pruritus during the 16-week treatment period (≥4-point reduction of weekly average of daily peak Pruritus NRS from baseline)
- Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
- Change from baseline to week 16 in percent BSA of AD involvement

Safety:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through end of treatment (week 16)
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through end of treatment (week 16)
- Incidence of treatment-emergent adverse events of special interest (AESIs) from baseline through end of treatment (week 16)
- Incidence of TEAEs from baseline through end of study (week 36)
- Incidence of treatment-emergent SAEs from baseline through end of study (week 36)
- Incidence of treatment-emergent AESIs from baseline through end of study (week 36)

Pharmacokinetic:

- Concentrations of functional REGN3500 in serum by treatment regimen at each assessment timepoint from baseline to end of study (week 36)

Any exploratory endpoints will be described in the statistical analysis plan (SAP).

Note: The safety and PK endpoints will not be included in the testing hierarchy.

4.3. Pharmacokinetic Variables

Pharmacokinetic sampling will be limited and focus on the pre-dose concentration of REGN3500.

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include ADA response status against REGN3500 and titer as follows:

- Pre-existing immunoreactivity
- Treatment-emergent ADA response
- Treatment-boosted ADA response
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)

5. Study Design

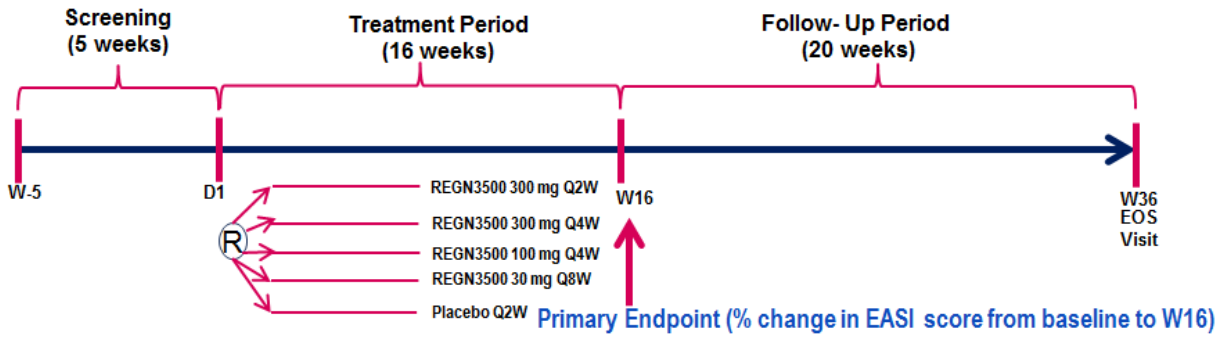
5.1. Study Description and Duration

This is a randomized, double-blind, placebo-controlled, double-dummy, parallel group study to assess the dose-response profile of various REGN3500 monotherapy dosing regimens in adult patients with moderate-to-severe AD. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. Approximately 60 patients per treatment group will be randomized with approximately 300 patients enrolled from approximately 100 multinational study sites.

After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 5 weeks (ie, 35 days) prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements (see Section 6.2). Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, medication use, concomitant illness, medical condition), unless the reason for the screen failure is related to failing the disease severity inclusion criteria.

Patients who meet eligibility criteria during the screening period will undergo day 1/baseline assessments. Patients who continue to meet eligibility criteria at baseline will be randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment regimens (REGN3500 300 mg SC Q2W, REGN3500 300 mg SC Q4W, REGN3500 100 mg SC Q4W, REGN3500 30 mg SC Q8W, or placebo SC Q2W) during the 16-week double-blind treatment phase (refer to Section 7 for additional information about study treatments) followed by a 20-week post-treatment follow-up period (Figure 1).

Figure 1: Study Flow Diagram



D: day; EASI: Eczema Area and Severity Index; EOS: end-of-study; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; R: randomization; W: week.

Patients will be required to apply moisturizers (bland emollients) at least twice daily for at least 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be the eighth day) and throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on any area(s) of lesional or non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Randomization will be stratified by baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD). It is planned that at least approximately 50% of patients randomized will have an IGA score of 4. To ensure enrollment according to intended distribution of disease severity, alerts will be built into the interactive voice response system/interactive web response system (IVRS/IWRS) to limit enrolling patients with an IGA score <4.

Patients will remain at the study site for a minimum of 30 minutes after administration of study drug, and the monitoring period may be extended up to 2 hours as per country-specific requirements. During the 16-week treatment period, patients will have study visits every other week. Safety laboratory tests, collection of samples for REGN3500 concentrations and ADA, biomarkers, and clinical assessments will be performed at specified clinic visits. The end-of-treatment (EOT) visit will occur at week 16, which is 2 weeks after the last dose of study drug. The primary endpoint will be evaluated at week 16.

Post-treatment follow-up visits will occur Q4W from week 20 through week 36. The duration of the 20-week post-treatment follow-up period is based on the time expected for REGN3500 drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of REGN3500. The 20-week post-treatment follow-up period corresponds to approximately 5 half-lives of REGN3500 (half-life ~30 days). The end-of-study (EOS) visit will occur at week 36.

Efficacy, safety, and laboratory assessments, and samples for REGN3500 concentration and potential ADA response to REGN3500, as well as research samples, will be performed or collected at specified time points throughout the study.

Samples for DNA and RNA analysis will also be collected from patients.

5.1.1. Study Stopping Rules

The independent Data Monitoring Committee (DMC) will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of REGN3500 (see more detail in Section 5.3.1). If at any time the DMC has significant concerns regarding a meaningful imbalance in TEAEs, treatment-emergent SAEs, or treatment-emergent AESIs, the DMC may make a recommendation to the sponsor to halt the study or make other changes in study conduct. This will prompt a review by the sponsor who will make a decision to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

5.1.2. End of Study Definition

The end of the study for this study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

No interim analysis is planned, but may be conducted at a future date. An unblinded primary analysis of the study may be performed once all patients in the study have completed the 16-week treatment period as specified in the protocol (week 16 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this primary analysis of the study will be considered the final analysis for the primary and secondary efficacy endpoints. Unblinded PK and ADA data through week 16 would also be included in this analysis.

A description of the statistical methods to be employed and blinding implications are in Section 10.4.3 and Section 10.4.3.1.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An independent DMC, composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data and perform a risk-benefit assessment.

The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The DMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the DMC are described in the DMC charter.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 300 patients will be randomized (60 per treatment group) from approximately 100 multinational study sites.

6.2. Study Population

The study population consists of adult (≥18 to 75 years of age) male or female patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatments are medically inadvisable (eg, intolerance, other important side effects or safety risks).

6.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female, 18 to 75 years
2. Chronic AD, according to American Academy of Dermatology Consensus Criteria (Eichenfield, 2014), that has been present for at least 3 years before the screening visit
3. EASI score ≥16 at the screening and baseline visits
4. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and baseline visits
5. ≥10% BSA of AD involvement at the screening and baseline visits
6. Baseline peak Pruritus NRS score for maximum itch intensity ≥4
   NOTE:
   - Baseline peak Pruritus NRS score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 35-day maximum duration for screening.
7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s) or for whom topical treatments are medically inadvisable (eg, intolerance, because of important side effects, or safety risks).
   NOTE:
   - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of topical corticosteroids (TCS) of medium to higher potency (± topical calcineurin inhibitor [TCI] as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.

- Patients with documented systemic treatment for AD (eg, systemic immunosuppressant drugs like cyclosporine, methotrexate, corticosteroids, etc) in the past 6 months are also considered to be inadequate responders to topical treatments and are potentially eligible for treatment with REGN3500 after appropriate washout.
- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician.
- Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be offered a course of treatment with a daily regimen of TCS of medium or higher potency (±TCI as appropriate), applied for at least 28 days during the screening period, or for the maximum duration recommended by the product prescribing information, whichever is shorter. Patients who demonstrate inadequate response during this period, as defined above, will be eligible for inclusion in the study following appropriate washout.

8. Have applied a stable dose of topical bland emollient (moisturizer) at least twice daily for at least the 7 consecutive days immediately before the baseline visit (ie, baseline/randomization visit would be the eighth day; see exclusion criterion 7 regarding restrictions on the kind of emollients permitted during the study).
9. Willing and able to comply with all clinic visits and study-related procedures
10. Provide informed consent signed by study patient or legally acceptable representative
11. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Participation in a prior anti-IL-33 class medication clinical study
2. Body mass index <16 kg/m^2
3. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
4. Having used any of the following treatments within 4 weeks before the baseline visit or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:
   - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc)
   - Phototherapy for AD
5. Treatment with TCS, TCI, or topical crisaborole within 1 week before the baseline visit

6. Treatment with biologics as follows:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer
    - Other biologics (including dupilumab): within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
7. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)
8. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
9. Planned or anticipated use of any prohibited medications and procedures during study treatment
10. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be re-screened after infection resolves
12. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB]*, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment * Patients with a positive TB QuantiFERON test result at screening will be excluded from the study.
13. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
14. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (HCV Ab) at the screening visit
15. At baseline, presence of any conditions listed as criteria for study drug discontinuation
16. Presence of skin comorbidities that may interfere with study assessments
17. History of cancer, with the exceptions of:
    - Patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix
    - Patients with other malignancies that have been successfully treated for >10 years prior to screening where, in the judgement of both the investigator and the treating physician, appropriate follow-up has revealed no evidence of recurrence through time of screening.

18. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization
19. History of alcohol or drug abuse within 2 years of the screening visit
20. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (hemoglobin A1c [HbA1c] ≥9%), patients with uncontrolled cerebrocardiovascular conditions (eg, myocardial infarction, unstable arterial hypertension, unstable angina, cerebrovascular accident, and stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg., demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc)
21. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical study, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc)
22. Planned or anticipated major surgical procedure during the patient's participation in this study
23. Patient is a member of the investigational team or his/her immediate family
24. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
25. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 20 weeks after the last dose of study drug. Highly effective contraceptive measures include:
    a. stable use of oral contraceptives associated with inhibition of ovulation (such as contraceptives containing estrogen/progesterone or high dose progesterone) initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner with confirmed sterility (ie, patient's medical record)
    e. and/or sexual abstinence†, ‡.

f. contraception for male patients is not required§

* Postmenopausal women must be amenorrheic for at least 12 months (without an alternative medical cause) in order not to be considered of childbearing potential. Amenorrheic status should be confirmed by demonstrating follicle-stimulating hormone levels (FSH) consistent with postmenopausal status according to laboratory ranges. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

§ Based on the known target biology of the study drugs and the extremely low levels of study drug expected to reach the fetus via seminal fluid, the use of contraception in treated males to prevent female partner and/or fetal exposure is considered unnecessary.

26. Known sensitivity to doxycycline and/or tetracycline or to any of the components of the investigational product formulation.
27. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from this study (as required by country regulations).

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.4.2.

6.4. Replacement of Patients

Patients prematurely discontinued from study or study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

REGN3500 is supplied in vials as a lyophilized powder. Each vial is reconstituted with 2.5 mL sterile Water For Injection, resulting in 2.0 mL withdrawable volume of 100 mg/mL REGN3500. Placebo that matches REGN3500 (REGN3500-matching placebo) is prepared in the same formulation as REGN3500 but without the addition of protein (ie, active substance, anti-IL-33 mAb). REGN3500 300 mg (or matching placebo) is administered as one 2.0 mL injection and one 1.0 mL injection, REGN3500 100 mg (or matching placebo) as one 1.0 mL injection, and REGN3500 30 mg (or matching placebo) as one 0.3 mL injection.

Study drug (REGN3500, REGN3500-matching placebo) will be prepared by an unblinded pharmacist (or qualified designee) and administered SC by a blinded study nurse (or other qualified study personnel) on day 1/baseline and then as noted below through week 14. The last dose of study treatment will be administered at week 14. Patients will be monitored at the study site for a minimum of 30 minutes after each administration of study drug, and the monitoring period may be extended up to 2 hours as per country-specific requirements.

Patients will be randomly assigned 1:1:1:1:1 to receive one of the following treatment regimens:

Table 1: Dosing Regimens

Dose Regimen	Injections During Visit	Study Drug Administered	Injection Volume (mL)
Day 1 (Visit 2) and Week 8 (Visit 6)			
REGN3500 300 mg SC Q2W	3	Placebo	0.3
		REGN3500	1.0
		REGN3500	2.0
REGN3500 300 mg SC Q4W	3	Placebo	0.3
		REGN3500	1.0
		REGN3500	2.0
REGN3500 100 mg SC Q4W	3	Placebo	0.3
		REGN3500	1.0
		Placebo	2.0
REGN3500 30 mg SC Q8W	3	REGN3500	0.3
		Placebo	1.0
		Placebo	2.0
Placebo SC Q2W	3	Placebo	0.3
		Placebo	1.0
		Placebo	2.0
Weeks 2 (Visit 3), 6 (Visit 5), 10 (Visit 7), and 14 (Visit 9)			
REGN3500 300 mg SC Q2W	2	REGN3500	1.0
		REGN3500	2.0
REGN3500 300 mg SC Q4W	2	Placebo	1.0
		Placebo	2.0
REGN3500 100 mg SC Q4W	2	Placebo	1.0
		Placebo	2.0
REGN3500 30 mg SC Q8W	2	Placebo	1.0
		Placebo	2.0
Placebo SC Q2W	2	Placebo	1.0
		Placebo	2.0

Dose Regimen	Injections During Visit	Study Drug Administered	Injection Volume (mL)
Weeks 4 (Visit 4) and 12 (Visit 8)			
REGN3500 300 mg SC Q2W	2	REGN3500	1.0
		REGN3500	2.0
REGN3500 300 mg SC Q4W	2	REGN3500	1.0
		REGN3500	2.0
REGN3500 100 mg SC Q4W	2	REGN3500	1.0
		Placebo	2.0
REGN3500 30 mg SC Q8W	2	Placebo	1.0
		Placebo	2.0
Placebo SC Q2W	2	Placebo	1.0
		Placebo	2.0

SC: subcutaneous; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks.

Note: All patients will receive Q2W SC injections. For the REGN3500 300 mg SC Q4W group, REGN3500 100 mg SC Q4W group, and REGN3500 30 mg SC Q8W group, there will be SC injection(s) of placebo in between REGN3500 doses so the injection frequency will match the other 2 groups (REGN3500 300 mg SC Q2W and placebo SC Q2W)

Instructions on dose preparation and administration are provided in pharmacy manual.

Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms, so that the same site is not injected for 2 consecutive visits. During the same dose administration, each injection must be given in a different anatomical location (eg, 1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc). To allow for adequate assessment of possible injection site reactions (ISRs), study drug should be administered only into areas of normal-looking skin. Instructions for recording and reporting ISRs will be provided in the study reference manual/site binder or file.

7.2. Background Treatment

All patients must apply moisturizers (bland emollients) at least twice daily for at least 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be the eighth day) and throughout study participation. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on any area(s) of lesional or non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue using stable doses of such moisturizers if initiated before the screening visit.

Patients will report compliance with background treatment (bland emollients) during the study using an electronic patient diary (e-diary).

Background treatment (bland emollients) is not provided by the sponsor.

7.3. Rescue Treatment

If medically necessary (ie, to control intolerable AD symptoms), patients may receive rescue treatment for AD at the discretion of the investigator. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical corticosteroids or topical crisaborole treatment may also be used as rescue treatment. Topical calcineurin inhibitors may also be used for rescue, but should be reserved for problem areas only (eg, face, neck, intertriginous and genital areas, etc). If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc), study treatment will be permanently discontinued immediately. Treatment will remain blinded for these patients.

Unless permanently discontinued from the study, all patients will complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

Rescue treatment is not provided by the sponsor.

7.4. Dose Modification and Study Treatment Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug but who do not withdraw from the study will be asked to return to the clinic for all remaining study visits and assessments per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2 (Early Termination [ET]).

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug injection
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy

- Any infection that:
  - Requires parenteral treatment with antibiotic or oral or parenteral treatment with anti-fungal, anti-viral, anti-parasitic, or anti-protozoal agent
  - Requires oral treatment with antibiotic for longer than 14 days.
  - Is opportunistic, such as TB or other infections whose nature or course may suggest an immuno-compromised status
- Severe laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.0 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3 × upper limit of normal (ULN) and total bilirubin >2×ULN, excluding confirmed Gilbert's Syndrome
  - AST and/or ALT >5×ULN (for more than 2 weeks)
  - Creatine phosphokinase (CPK) >20×ULN

  NOTE:
  If the laboratory abnormality is considered causally related to study drug, study treatment will be permanently discontinued. In cases in which a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident), study treatment will be suspended but it may be resumed when the laboratory abnormality is sufficiently normalized. A decision to resume study treatment will be made jointly by the investigator and medical monitor (medical monitor's written approval is required).
- Patient withdraws consent
- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Treatment with a live (attenuated) vaccine
  - Treatment with any prohibited concomitant medication or procedure (see Section 7.7.1).

    NOTE:
    Study drug does not need to be discontinued if a patient receives prohibited topical medication as rescue treatment (Section 7.3 and Section 7.7.2.1).

The investigator may discontinue study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation.

7.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily discontinued in the event of:

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count $\leq 1.5\times10^3/\mu L$ but $>1.0\times10^3/\mu L$
  - Platelet count $\leq 100\times10^3/\mu L$ but $>50\times10^3/\mu L$
  - CPK >10×ULN but ≤20×ULN
- Other intercurrent major illnesses requiring hospitalization or major surgery
- Treatment with a prohibited concomitant medication or procedure (Section 7.7.1).
  NOTE:
  Study drug does not need to be discontinued if a patient receives prohibited topical medication as rescue treatment (Section 7.3 and Section 7.7.2.1).

After the condition leading to suspension of dosing resolves, study treatment may resume at the discretion of the investigator in consultation with the medical monitor. A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor.

The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation.

7.5. Method of Treatment Assignment

On day 1/baseline, eligible patients will be randomized in a 1:1:1:1:1 ratio to receive double-blind treatment with REGN3500 SC 300 mg Q2W, REGN3500 SC 300 mg Q4W, REGN3500 SC 100 mg Q4W, REGN3500 SC 30 mg Q8W, or placebo SC Q2W according to a central randomization scheme provided by an IVRS/IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified according to baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD).

It is planned that at least approximately 50% of patients randomized will have an IGA score of 4. To ensure enrollment according to intended distribution of disease severity, alerts will be built into the IVRS/IWRS to limit enrolling patients with an IGA score <4.

Patients who are permanently discontinued from study drug will not be replaced.

7.5.1. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a medication numbering system will be used. To maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody and study drug concentration results will not be communicated to the sites, and the sponsor's clinical operational team will not have access to results associated with patient identification until after the final database lock. The bioanalytical analyst, bioanalytical team representatives, and clinical pharmacology representatives responsible for determining the study drug concentration measurements, ADAs, and biomarkers will not be blinded to the dosing information.

7.5.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The IVRS/IWRS will provide the treatment assignment to the investigator.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.5.3. Unblinding for Regulatory Reporting Purposes

Treatment assignments for certain patients may be unblinded to Pharmacovigilance personnel for the purpose of regulatory reporting of suspected unexpected serious adverse reactions (SUSARs).

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

7.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study drug:

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

Patients will be dosed under the supervision of appropriate study personnel. All study drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.7. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

Information on concomitant medication for each patient will be recorded at each study visit from screening through the end of study.

7.7.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study. Study drug will be immediately discontinued if any of the following are used during the study (see Section 7.4.2.1):

- Treatment with a live (attenuated) vaccine (a list of examples of such vaccines is below):
  - Chickenpox (Varicella)
  - FluMist-Influenza
  - Intranasal influenza
  - Measles (Rubeola)

  - Measles-mumps-rubella combination
  - Measles-mumps-rubella-varicella combination
  - Mumps
  - Oral polio (Sabin)
  - Oral typhoid
  - Rubella
  - Smallpox (Vaccinia)
  - Yellow fever
  - Bacillus Calmette-Guerin
  - Rotavirus
  - Varicella Zoster (shingles; ie, Zostavax)
- Treatment with an investigational drug (other than REGN3500)
- Treatment with immunomodulating biologics
- Treatment with systemic non-steroidal immunosuppressant (may be used as rescue, see Section 7.3 for details)
- Treatment with systemic corticosteroids (may be used as rescue, see Section 7.3 for details)
- Treatment with TCS or TCI (may be used as rescue in which study drug will not be discontinued, see Section 7.3 for details)
- Treatment with topical crisaborole (may be used as rescue in which study drug will not be discontinued, see Section 7.3 for details)
- Initiation of treatment of AD with prescription moisturizers

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy (ultraviolet A [UVA], ultraviolet B [UVB], narrowband UVB [nbUVB], high dose UVA, and psoralen and UVA [PUVA])
- Tanning in bed/booth

7.7.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 7.7.1, treatment with concomitant medications are permitted during the study. This includes basic skin care (cleansing and bathing, including bleach baths), bland emollients (required as background treatment; however, bland emollients should not be applied on any area(s) of lesional or non-lesional skin designated for assessment for at least 8 hours before each clinic visit), topical anesthetics, and antihistamines for any duration, and oral antibiotics for up to 14 days. Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted; if there is any question regarding whether

a concomitant medication may be used during the study, the study site should contact the medical monitor.

7.7.2.1. Prohibited Concomitant Medications or Procedures as Rescue Treatment

If medically necessary (ie, to control intolerable AD symptoms), study patients may receive rescue treatment for AD at the discretion of the investigator (see Section 7.3). If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs, study treatment will be permanently discontinued immediately. If rescue treatment consists of topical medications, the patient can continue study treatment.

Blinded adjudication of concomitant medications may be performed to identify concomitant medications that confound study endpoints.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 2.

Table 2: Schedule of Events

	Screening Period[13, 14]	Double-Blind Treatment Period									Follow-Up Period						
In-clinic Visit (V) **Study Procedure[1]**	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EOT V10**	**V11**	**V12**	**V13**	**V14**	**EOS V15**	**Un-sch[16]**	**ET [19]**
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W20	W24	W28	W32	W36	-	-
Day (D)	D−35 to D−1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D141	D169	D197	D225	D253	-	-
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-
Screening/Baseline:[1]																	
Inclusion/Exclusion	X	X															
Informed Consent	X																
Medical History/ Demographics	X																
Ocular History[8]	X																
Patient e-diary Training (Pruritus, Pain, and Sleep Quality NRS Assessments and Emollient Use)[2]	X																
Randomization		X															
Treatment:[1]																	
Review patient e-diary data		X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration/ Dispensing/ Accountability[3]		X	X	X	X	X	X	X	X								
Concomitant Meds/ Procedures	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[1]																	
Pruritus, Pain, and Sleep Quality NRS (daily)[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-reported HADS, DLQI, POEM[5,6]	X	X	X	X		X		X		X		X		X	X	X	X
EASI, IGA, GISS, SCORAD, BSA[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening Period[13, 14]	Double-Blind Treatment Period									Follow-Up Period						
In-clinic Visit (V) **Study Procedure[1]**	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EOT V10**	**V11**	**V12**	**V13**	**V14**	**EOS V15**	**Un-sch[16]**	**ET [19]**
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W20	W24	W28	W32	W36	-	-
Day (D)	D−35 to D−1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D141	D169	D197	D225	D253	-	-
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-
Safety:[1]																	
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X									X					X	X	X
ECG	X									X					X	X	X
Weight	X	X								X					X	X	X
Height	X																
Ophthalmological Exam[8]	X															X[17]	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[18]	X
Laboratory Testing:[1,11]																	
Hematology, Chemistry	X	X		X		X		X		X	X	X	X	X	X	X	X
Serologies (HIV Ab, HBsAg, HBcAb, HCV Ab)	X																
TB QuantiFERON Testing [9]	X																
Serum FSH (confirm menopausal status)	X																
Pregnancy Test (WOCBP only)[10]	Serum	Urine		Urine		Uri-ne		Urine		Ser-um	Urine	Urine	Urine	Urine	Ser-um	Uri-ne	Ser-um
Urinalysis	X	X		X		X		X		X		X		X	X	X	X
PK and ADA Samples:[1, 11]																	
Serum REGN3500 Concentration (PK)		X	X	X		X		X		X	X	X	X	X	X	X[18]	X
Anti-REGN3500 Antibody (ADA)[20]		X								X					X	X[18]	X
Biomarkers:[1, 11]																	
hs-CRP, SAA	X	X		X		X		X		X				X	X	X	X
TARC	X	X		X		X		X		X				X	X	X	X
Total IgE	X	X		X						X					X	X	X
Total IL-33		X	X	X		X		X		X	X	X	X	X	X	X	X
FBR Samples (serum/plasma)	X	X		X		X		X		X				X	X	X	X

	Screening Period[13, 14]	Double-Blind Treatment Period									Follow-Up Period						
In-clinic Visit (V) **Study Procedure[1]**	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EOT V10**	**V11**	**V12**	**V13**	**V14**	**EOS V15**	**Un-sch[16]**	**ET [19]**
Week (W)	-	-	W2	W4	W6	W8	W10	W12	W14	W16	W20	W24	W28	W32	W36	-	-
Day (D)	D−35 to D−1	D1	D15	D29	D43	D57	D71	D85	D99	D113	D141	D169	D197	D225	D253	-	-
Visit Window in Days	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-
Genomics Sample:[1, 11]																	
Whole Blood DNA[12]		X															
Whole Blood RNA[12]		X								X					X		X

ADA: anti-drug antibody; BSA: body surface area; D: day; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; ECG: electrocardiogram; e-diary: electronic patient diary; EOS: end-of-study; EOT: end-of-treatment; ET: early termination; FBR: Future Biomedical Research; FSH: follicle-stimulating hormone; GISS: Global Individual Signs Score; HADS: Hospital Anxiety and Depression Scale; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; HIV Ab: human immunodeficiency virus antibody; hs-CRP: high-sensitivity C-reactive protein; ICF: informed consent form; IGA: Investigator's Global Assessment; IgE: immunoglobulin E; IL: interleukin; Meds: medications; NRS: Numerical Rating Scale; PK: pharmacokinetic; POEM: Patient Oriented Eczema Measure; SAA: serum amyloid A; SCORAD: SCORing Atopic Dermatitis; TARC: thymus and activation-regulated chemokine (CCL17); V: visit; Unsch: unscheduled visit; W: week; WOCBP: women of childbearing potential.

8.1.1. Footnotes for the Schedule of Events Table

1. Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments (including sample collection for ADA, PK, biomarkers, DNA, and RNA), and then administration of study drug.
2. Training of patients regarding completion of e-diary to record (1) completion of assessment of Pruritus, Pain, and Sleep Quality NRS scales and (2) emollient usage.
3. All patients will receive Q2W SC injections. For the REGN3500 300 mg SC Q4W group, REGN3500 100 mg SC Q4W group, and REGN3500 30 mg SC Q8W group, in order to maintain the blinding, there will be SC injection(s) of placebo in between REGN3500 doses so the injection frequency will match the other 2 groups (REGN3500 300 mg SC Q2W and placebo SC Q2W) (see randomization and dosing regimen in Section 7.1 Table 1). Patients will be closely monitored at the study site at visits 2 through 9 (day 1 through week 14) for a minimum of 30 minutes after the administration of study drug, and the monitoring period may be extended up to 2 hours as per country specific requirements. In addition to the predose assessments, patients will be assessed for adverse events (AEs) at 30 minutes (±10 minutes) postdose or until the end of the monitoring period (if applicable).
4. Pruritus, Pain, and Sleep Quality NRS will be completed daily via electronic questionnaire (e-diary). Reporting of these data begins the evening of visit 1 (screening).
5. Questionnaires will be completed before any other assessments or invasive procedures (blood draws, study drug injection, etc).
6. The questionnaires will be administered only to the subset of patients who speak fluently the language in which the questionnaire is presented (based on availability of validated translations in participating countries).
7. Vital signs (sitting blood pressure, pulse, and respiratory rate) should be taken predose and 30 minutes (±10 minutes) postdose. In addition, body temperature should be taken predose.
8. Ophthalmological exams at screening are limited to those patients who have a history of certain eye disorders (conjunctivitis, blepharitis or keratitis) within the last 12 months. Exams must be performed by an ophthalmologist (preferably with expertise in Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert). Further evaluation will be performed including any additional tests, if applicable, as per the discretion of the ophthalmologist.
9. Tuberculosis QuantiFERON testing at screening will be performed.
10. Not required if postmenopausal status confirmed at screening.

11. Blood samples collected before the administration of study drug. Pharmacokinetic samples will be collected for the determination of REGN3500 concentration and ADA samples for the immunogenicity assessment of REGN3500. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional PK and ADA samples may be collected at or near the event. At the visits where ADA samples are to be taken, the sample should be collected with the PK sample.
12. One whole blood sample to extract DNA for pharmacogenomics analyses should be collected on day 1/baseline (visit 2), but can be collected at any visit. Whole blood samples for RNA extraction should be collected according to time points in Table 2.
13. Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, medication use, concomitant illness, medical condition), unless the reason for the screen failure is related to failing the disease severity inclusion criteria.
14. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements (see Section 6.2).
15. Clinical sites will check patient data collected on the e-diary. Baseline peak Pruritus NRS score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 35-day maximum duration for screening. Patients are also required to have applied a stable dose of topical bland emollient (moisturizer) at least twice daily for at least the 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be the eighth day).
16. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason (eg, before a rescue medication/procedure is used), as warranted.
17. Patients who experience adverse events of special interest (AESIs) related to eye disorders (refer to Section 9.4.3) must be referred to an ophthalmologist (preferably with expertise in Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert). Further evaluation of these AEs will be performed including any additional tests, if applicable, as per the discretion of the ophthalmologist.
18. If the unscheduled visit was due to an AE, collect samples for PK and ADA analysis.
19. Patients who are withdrawn from the study will be asked to return to the clinic for ET assessments.
20. In the event a patient sample is positive in the REGN3500 ADA assay at week 16 or the first time point analyzed, the week 4 PK sample may be analyzed in the ADA assay.

8.1.2. Early Termination Visit

Patients who permanently discontinue study drug but who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule (see Section 7.4.2 and Table 2). Patients who are withdrawn from the study will be asked to return to the clinic for ET assessments, only (Table 2).

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason (eg, before a rescue medication/procedure is used), as warranted (Table 2 and Section 8.1.1).

8.2. Study Procedures

Assessments/procedures should be conducted in the following order: patient reported outcomes, investigator assessments, safety and laboratory assessments and then administration of study drug. All questionnaires should be administered before any other assessments or invasive procedures (blood draws, study drug injection, etc).

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: obtaining informed consent, demographics, medical history (including diagnosis of chronic AD, prior treatments for AD, vaccination history for previous 6 months and history of other atopic diseases), height, human immunodeficiency antibody (HIV Ab), HBsAg, HBcAb, HCV Ab, TB QuantiFERON test, and serum FSH.

Patients will be trained on using electronic questionnaires (e-diary) at the screening visit (visit 1). Patients will record Pruritus NRS scores and compliance with background treatment (ie, bland emollients) during the study using an electronic questionnaire (e-diary) beginning the evening of the screening visit (visit 1).

8.2.2. Efficacy Procedures

8.2.2.1. Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a 24-hour recall period using an electronic questionnaire. Patients will be asked the following questions:

- For maximum itch intensity: “On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being the ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?”

Patients will be instructed on using an electronic questionnaire to record their Pruritus NRS score at the screening visit. Patients will complete the rating scale DAILY through the entire study (screening, treatment, and follow-up periods). Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

8.2.2.2. Peak Pain Numeric Rating Scale (NRS)

The Peak Pain NRS is a simple assessment tool that patients will use to report the intensity of their pain during a 24-hour recall period using an electronic questionnaire. Patients will be asked answer to the following question on a scale from 0 (no pain) to 10 (worst pain possible):

> For the question below, think about all the areas of your skin with eczema.
>
> "How would you rate your skin pain at its worst in the previous 24 hours?"

Patients will be instructed on using an electronic questionnaire to record their Peak Pain NRS score at the screening visit. Patients will complete the rating scale DAILY through the entire study (screening, treatment, and follow-up periods). Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

8.2.2.3. Sleep Quality Numeric Rating Scale (NRS)

The Sleep Quality NRS is a simple assessment tool that patients will use to report the quality of their sleep during a 24-hour recall period using an electronic questionnaire. Patients will be asked the following question on a scale of 0 (best possible sleep) to 10 (worst possible sleep) upon awakening for the day:

> "Thinking about all the ways eczema affects your sleep, select the number that best describes your sleep last night."

Patients will be instructed on using an electronic questionnaire to record their Sleep Quality NRS score at the screening visit. Patients will complete the rating scale DAILY through the entire study (screening, treatment, and follow-up periods). Clinical sites will check patient data collected using an e-diary for protocol compliance and remind patients to complete their e-diary throughout the study.

8.2.2.4. Hospital Anxiety Depression Scale (HADS)

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond, 1983) (Herrmann, 1997) (Bjelland, 2002). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. The questionnaire will be administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Table 2.

The HADS is provided in the study reference manual/site binder or file.

8.2.2.5. Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical studies to assess the impact of AD disease symptoms and treatment on QOL (Badia, 1999). The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL. The questionnaire will be administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Table 2.

The DLQI is provided in the study reference manual/site binder or file.

8.2.2.6. Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical studies to assess disease symptoms in children and adults (Charman, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0=no days, 1=1 to 2 days, 2=3 to 4 days, 3=5 to 6 days, and 4=all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity. The questionnaire will be administered only to the subset of patients who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries), at time points according to Table 2.

The POEM is provided in the study reference manual/site binder or file.

8.2.2.7. Investigator's Global Assessment (IGA)

The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed at time points according to Table 2.

The IGA is provided in the study reference manual/site binder or file and in Appendix 1.

8.2.2.8. Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical studies to assess the severity and extent of AD (Hanifin, 2001). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). The EASI will be collected at time points according to Table 2.

The EASI assessment tool is provided in the study reference manual/site binder or file.

8.2.2.9. Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each major section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Patients will undergo this assessment at time points according to Table 2.

The BSA assessment tool is provided in the study reference manual/site binder or file.

8.2.2.10. Global Individual Signs Score (GISS)

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria. The GISS will be assessed at time points according to Table 2.

The GISS assessment tool is provided in the study reference manual/site binder or file.

8.2.2.11. SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD (Dermatology, 1993). There are 3 components to the assessment: A extent or affected body surface area, B=severity, and C=subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see Section 8.2.2.9) and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analog scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: $A/5 + 7B/2 + C$ where the maximum is 103. Patients will undergo this assessment at time points according to Table 2.

The SCORAD assessment tool is provided in the study reference manual/site binder or file.

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

Vital signs (sitting blood pressure, pulse, and respiration rate) should be taken predose and 30 minutes (±10 minutes) postdose (see Table 2). In addition, body temperature should be taken predose.

8.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

8.2.3.3. Body Weight and Height

Body weight and height will be measured at time points according to Table 2 .

8.2.3.4. Electrocardiogram

Electrocardiograms (ECGs) should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Table 2. The ECG strips or reports will be retained with the source and the results will be documented in the electronic CRF (eCRF).

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the study reference manual/site binder or file.

8.2.3.5. Laboratory Testing

Hematology, chemistry (including the CPK, ALT, AST, and lactate dehydrogenase [LDH] samples), urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. In addition to collecting blood and urine samples to measure overall patient health, total basophil and eosinophil counts are of particular interest in AD patients due to the occurrence of basophil histamine release and eosinophilia in this population. Understanding the lymphocyte profiles of AD patients may help researchers understand disease heterogeneity.

Detailed instructions for sample collection are in the study reference manual/site binder or file provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total and indirect bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen	Triglycerides
Carbon dioxide	AST	Uric acid
Calcium	ALT	CPK
Glucose	Alkaline phosphatase	
Albumin	LDH	

*(low-density lipoprotein and high-density lipoprotein)

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Pregnancy Testing

Pregnancy testing (serum human chorionic gonadotropin [hCG] or urine hCG) will be performed for all WOCBP at visits according to Table 2.

Other Laboratory Tests

The following other laboratory tests will be performed at screening: HIV, HBsAg, HBcAb, HCV Ab, and TB QuantiFERON test.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study drug or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.3.6. Research Samples

Research samples (serum/plasma) will be collected at visits according to Table 2.

Use and Storage of Research Samples (Serum/Plasma)

Research serum and plasma samples will be collected to study IL-33 and IL-4/IL-13 pathways, effect of IL-33 and IL-4Rα inhibition with a mAb. In addition, samples may be used to study immunology, inflammation, and atopic diseases. Remaining samples may be stored for future use in experiments related to the above mentioned scope of research. If necessary, the samples may also be used to identify markers associated with toxicity or predictive of efficacy. Data from these analyses will not be reported in the clinical study report (CSR).

8.2.3.7. Ophthalmologic (Eye) Examinations

Patients who have a history of certain eye disorders (conjunctivitis, blepharitis, or keratitis) within the last 12 months of the screening visit will be referred during screening to an ophthalmologist (preferably with expertise in treating Cornea and External Eye Disease [‘front-of-the-eye’] subspecialty expert).

Patients who experience AESIs related to eye disorders (refer to Section 9.4.3 will also be referred to an ophthalmologist (preferably with expertise in treating patients or Cornea and External Eye Disease ['front-of-the-eye'] subspecialty expert). Further evaluation of these AESIs will be performed including any additional tests, if applicable, as per the discretion of the ophthalmologist.

8.2.4. Drug Concentration and Measurements

Samples for study drug concentration will be collected at visits listed in Table 2. The PK sample should be taken with the ADA sample when both are on the same day.

Any unused samples may be used for exploratory biomarker research.

8.2.5. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 2. At the visits where ADA samples are to be taken, the sample should be collected with the PK sample. Anti-drug antibody and PK samples are to be collected prior to administration of study drug.

In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional ADA samples may be collected at or near the event.

Any unused samples may be used for exploratory biomarker research.

8.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how REGN3500 may modify the underlying disease process in AD. In particular, the role of IL-33 and the effect of REGN3500 on thymus and activation-regulated chemokine (CCL17; TARC), total serum IgE, total IL-33, high sensitivity C-reactive protein (hs-CRP), and serum amyloid A (SAA) will be explored.

Biomarker samples will be collected at time points according to Table 2. Biomarker measurements will be performed in serum and plasma samples to determine effects on biomarkers of AD or relevant physiological and pathogenic processes. The biomarkers studied are believed to be relevant to the pathophysiology of indication target engagement, mechanism of action of REGN3500 and possible toxicities. Pharmacodynamic analysis will be described in the SAP and the results will be described in the CSR.

8.2.6.1. Thymus and Activation-Regulated Chemokine (CCL17; TARC)

The biomarker TARC is a chemokine induced by IL-4/IL-13, shown to be strongly associated with disease severity in AD, and may be involved in pathogenesis of the disease. Baseline TARC levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for PD effects of study treatment on TARC.

TARC will be measured in serum from samples collected at time points indicated in Table 2. Detailed instructions for blood sample collection are provided in the study reference manual/site binder or file. Data analysis will be described in the SAP and the results will be described in the CSR.

8.2.6.2. Total Immunoglobulin E (IgE)

Patients with AD often have elevated IgE. Total IgE levels have been found to modestly correlate with AD severity, and may be involved in the pathogenesis of the disease. Changes in total IgE reflects not only on AD, but atopy in general. Baseline IgE levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for PD effects of study treatment on total IgE.

Total IgE will be measured in serum from samples collected at time points indicated in Table 2. Detailed instructions for blood sample collection are provided in the study reference manual/site binder or file. Data analysis will be described in the SAP and the results will be described in the CSR.

8.2.6.3. Total Interleukin-33 (IL-33)

Total IL-33 is a measure of target engagement for REGN3500. Total IL-33 will be measured in serum from samples collected at time points indicated in Table 2. Data analysis will be described in the SAP and the results will be described in the CSR.

8.2.6.4. High-Sensitivity C-Reactive Protein (hs-CRP)

C-reactive protein (CRP) is a biomarker of Type 1 inflammation. High-sensitivity CRP, which is more precise than standard CRP, can be used to measure of chronic inflammation or detect low-grade inflammation.

Baseline hs-CRP levels may be assessed for potential predictive value for treatment response. Post-treatment samples may be evaluated for effects of study treatment on hs-CRP. High-sensitivity CRP may be measured in plasma from samples collected at time points indicated in Table 2. Detailed instructions for blood sample collection are provided in the study reference manual/site binder or file. Data analysis will be described in the SAP and the results will be described in the CSR.

8.2.6.5. Serum Amyloid A (SAA)

Serum amyloid A is an early and sensitive blood biomarker for tissue injury and Type 1 inflammation and has been indicated in many inflammatory diseases. The level of SAA circulating in the blood is known to increase dramatically in response to tissue damage or inflammation, classifying it as an acute phase protein

Serum amyloid A may be measured in samples collected at time points indicated in Table 2. Detailed instructions for sample collection are provided in the study reference manual/site binder or file. Data analysis will be described in the SAP and the results will be described in the CSR.

8.2.7. Future Biomedical Research (FBR)

The unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for Future Biomedical Research (FBR) of AD, REGN3500 and its pathway and related diseases. Additional samples will be collected for FBR. After 15 years, any residual samples will be destroyed. The results of these FBR analyses will not be presented in the CSR.

8.2.7.1. Pharmacogenomics Analysis

Whole blood samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points according to Table 2.

DNA and RNA samples will be collected for the pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of AD and related diseases. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomics analyses which the sponsor is unable to comply with, samples will not be collected from patients at the site.

The purpose of the pharmacogenomics analyses is to identify genomic associations with clinical or biomarker response to REGN3500, other AD clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of AD as well as related allergic/atopic diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or AD and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients, according to local regulations. This may include death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, according to local regulations.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (ie, SUSAR), to the health authorities, ECs/IRBs as appropriate, and to the investigators (in a blinded manner).

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of symptoms related to AD which occur during the screening period prior to study drug administration will be considered expected.

In addition, the sponsor will report in all other SAEs to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the study in the CSR to health authorities and ECs/IRB as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the EOS visit. Refer to study reference manual/site binder or file for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual/site binder or file for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the EOS visit or within 140 days of last study drug administration if the patient early terminated from the study - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the EOS/ET visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female during the study or within 140 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Mycosis fungoides or other forms of cutaneous T-cell lymphoma
- Any severe infection; any infection requiring treatment with parenteral antibiotics/anti-viral/anti-fungal agent; any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks; any clinical endoparasitosis; any opportunistic infection

Note:
Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESIs.

- Conjunctivitis (any type or etiology), keratitis, or blepharitis (only events that are either severe or serious or lasting ≥4 weeks will be reported as AESIs)

Any patient who experiences an AESI related to an eye disorder will be referred to an ophthalmologist. Further evaluation of these AESIs will be performed including any additional tests, as per the discretion of the ophthalmologist.

- Significant ALT elevation
  - ALT >3×ULN associated with total bilirubin >2×ULN; or
  - ALT >5×ULN in patients with baseline ALT ≤2×ULN; or
  - ALT >8×ULN if baseline ALT >2×ULN

Refer to the study reference manual/site binder or file for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

Refer to the study reference manual/site binder or file for the procedures to be followed.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the Medical/Study Director in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions (ISRs)

The severity of ISRs will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the "blinded" investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition

- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the "blinded" investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study conduct?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the course of the study
- do not reappear or worsen when dosing with study participation is resumed

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the course of the study.
- resolve or improve after discontinuation from study participation.
- reappear or worsen when study participation is resumed

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical study, as well as in any other clinical study using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

10. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

For efficacy endpoints, the analyses will be the comparisons of the REGN3500 and the placebo groups. The following null and alternative hypotheses of the primary endpoint will be tested for each REGN3500 group and the placebo group:

H0: No treatment difference between REGN3500 and placebo.

H1: There is treatment difference between REGN3500 and placebo.

To control the overall family-wise type I error rate of 5%, a hierarchical procedure from high to low dose will be performed for the primary endpoint and selected secondary efficacy endpoints (eg, EASI-75, IGA score of 0 or 1 and a reduction from baseline of ≥2 points responder at week 16) across the REGN3500 dose regimens vs placebo. The final hierarchy will be provided in the SAP that will be finalized prior to database lock.

10.2. Justification of Sample Size

For the primary endpoint, the enrollment of 60 patients per treatment group will provide 96% power to detect a 35% difference between the most efficacious REGN3500 SC dose and the placebo group with respect to percent change in EASI score from baseline to week 16, assuming the common standard deviation (SD) is 50%, with a 2-sided test at the 0.05 significance level. The 50% SD along with the 35% difference in the mean percent were estimated based on results from 2 phase 3 dupilumab AD studies (R668-AD-1334 and R668-AD-1416).

Recently, publicly available results disclosed from an uncontrolled phase 2a study evaluating a single IV dose of an anti-IL-33 mAb (ANB020, AnaptysBio) in 12 moderate-to-severe adult AD patients offer mechanistic support for anti-IL-33 approach to improving AD disease severity (Ogg, 2018). In this study, 83% of patients were reported to have achieved EASI-50 at day 29 and an average EASI reduction of 62% by day 57 following dosing.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Set

The full analysis set (FAS) includes all randomized patients; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients who received any study drug and who had at least 1 non-missing study drug concentration result following the first dose of study drug.

10.3.4. Pharmacodynamic Analysis Set

The PD analysis set population includes all randomized patients who received any study drug and who had at least 1 non-missing PD result following the first dose of study drug.

10.3.5. Anti-Drug Antibody Analysis Set

The ADA population includes all treated patients who received any amount of study drug (REGN3500 or REGN3500-matching placebo) and who had at least 1 non-missing ADA result following the first dose of study drug.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set (eg, FAS, provided in Section 10.3.1)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

10.4.3. Efficacy Analyses

The efficacy endpoints will be analyzed using the FAS which includes all randomized patients. Efficacy analyses will be based on the treatment allocated at randomization (as randomized).

Continuous endpoints will be analyzed using the multiple imputation (MI) method with analysis of covariance (ANCOVA) model, which includes treatment group, stratification variable (moderate [IGA=3] vs. severe [IGA=4] AD) and relevant baseline value as covariates. The efficacy data will be set to missing after rescue treatment is used, then all missing data from the FAS will be imputed 40 times under missing at random assumption to generate a complete dataset at each imputation by using the MI Statistical Analysis System (SAS) procedure. These complete datasets will be analyzed using an ANCOVA model and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.

Sensitivity analyses such as ANCOVA model with last observation carried forward, MI method with ANCOVA model on all observed data regardless of rescue treatment use will be conducted. Additional details on sensitivity analyses will be provided in the SAP.

The categorical endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline disease severity stratum.

Patients will be considered as non-responders at the time point where data are missing (regardless of reason for missingness, eg, due to drop-out or data set to missing after rescue treatment). In addition, several sensitivity analyses will be performed including using MI imputing missing value (eg, EASI score) to determine whether or not met criteria (eg, EASI 75) for binary endpoints. Additional details on sensitivity analyses will be provided in the SAP.

10.4.3.1. Primary Analysis of the Study

A primary analysis of the study may be performed when the last patient completes 16 weeks of treatment duration, in order to expedite the potential interactions with regulatory agencies to design future phase 3 studies. No changes in the conduct of the study will be made based on this primary analysis of the study. The assessment of primary and secondary endpoints specified in Section 4.2.1 and Section 4.2.2 performed during the analysis will be the final analysis of the primary endpoint and secondary endpoints. Hence there will be no need for alpha adjustment due to the primary analysis of the study.

If a decision is made to perform the primary analysis of the study, in order to maintain study integrity with respect to the post-treatment follow-up visits, safety visits and analyses, a dissemination plan will be written. This plan will clearly identify the unblinded team (including the statistician) that will perform the primary analysis of the study and all related activities, restrict other clinical team members and other sponsor personnel from access to individual patient treatment allocation and site level analysis results (ie, remain blinded), and ensure that the dedicated unblinded team will not participate in the data review or data decisions for the subsequent post-treatment analyses. However, the dedicated unblinded team can participate in the analysis following the final database lock.

10.4.4. Safety Analysis

The safety analysis will be based on the SAF. This includes reported TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results will be presented for each treatment group.

10.4.4.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to the end of study. The treatment-emergent period includes the 16-week treatment period and follow-up period.
  - Treatment period: date of the first dose of study drug to week 16 visit date (study day 113 starting from the first dose of study drug if week 16 visit date is unavailable) or ET date, whichever comes first.
  - Follow-up period: date after week 16 visit date (study day 113 starting from first dose of study drug if week 16 visit date is unavailable) to EOS visit.

Treatment-emergent AEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group and for overall during the treatment-emergent period, during the 16-week treatment period, and during the follow-up period will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent AEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.4.2. Other Safety

Vital Signs

Vital signs (body temperature and sitting blood pressure, pulse, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

The number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a PCSV at any postrandomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

12-Lead ECG

Electrocardiogram results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

10.4.4.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment and calculated as:

(date of last study drug injection – date of first study drug injection) + 14 days

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, Q1, medians, Q3, and maximums.

A summary of the number of doses by treatment group will be provided.

10.4.4.4. Treatment Compliance

The compliance with protocol-defined investigational product will be calculated as follows:

Treatment compliance=

(number of investigational product injections during exposure period)/(number of planned investigational product injections during exposure period) × 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

10.4.5. Pharmacokinetics

10.4.5.1. Analysis of Drug Concentration Data

No formal statistical analysis will be performed. Trough functional REGN3500 concentration in serum will be summarized at each time point using descriptive statistics. The data may be combined with data from other studies, as applicable, for analysis using population methods. Any population PK analysis will be reported separately.

10.4.6. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.4 will be summarized. Listings of treatment-emergent ADA and titers presented by patient, time point, and dose cohort (treatment group) will be provided. The incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by dose cohort and ADA titer level.

Association of treatment-emergent and treatment boosted ADA responses and titers with potential impact on PK, safety, or efficacy may be evaluated. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated.

10.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Biomarker results will be summarized by baseline, measured values, change from baseline and percent change from baseline to each scheduled assessment time with descriptive statistics. Other exploratory analyses may be performed, but will not be described in the SAP or CSR.

10.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid pre-first-dose assessment available.

General rules for handling missing data:

- Rules for handling missing data for assessment (other than efficacy)
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study drug, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study drug date, then the start date by the study drug intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC).

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an eCRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

Providing access to all necessary facilities, study data, and documents for the inspection or audit

Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately

Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.

- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

14.2. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.3. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC and health authority, if required by local regulation, approved amendment.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely. In the event of a close-out of a study site, no additional patients will be screened or enrolled. Patients who are currently enrolled in the study will be followed up according to the protocol (see Table 2).

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and health authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Investigating the Efficacy, Safety, and Pharmacokinetic Profiles of REGN3500 Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1: INVESTIGATOR'S GLOBAL ASSESSMENT (IGA) SCALE

Please refer to the instructions below and place a checkmark next to the appropriate score below:

_____ **0 Clear**
_____ **1 Almost Clear**
_____ **2 Mild Disease**
_____ **3 Moderate Disease**
_____ **4 Severe Disease**

_____	_____	_____
Print Name (First/Last) of Investigator Completing Assessment	**Signature**	**Date**

Instructions:

The Investigator's Global Assessment is a static 5-point measure of disease severity based on an overall assessment of the skin lesions.

IGA: Disease Severity Scale and Definitions of the scoring:

Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Proposed Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Investigating the Efficacy, Safety, and Pharmacokinetic Profiles of REGN3500 Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis

Protocol Number: R3500-AD-1805

Protocol Version: R3500-AD-1805 Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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