REGENERON
Biostatistics and Data Management

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STATISTICAL ANALYSIS PLAN
VERSION: FINAL V1.0

Clinical Study Protocol 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**

Compound:	REGN3500
Protocol Number:	R3500-AD-1805
Clinical Phase:	Phase 2b
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGOT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST (SGPT)	Aspartate aminotransferase
BAS	Biomarker analysis set
BSA	Body surface area
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
DFI	Dermatitis Family Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HLT	High Level Term
ICF	Informed consent form
ICH	International conference on harmonisation
IGA	Investigator global assessment
IL	Interleukin
IgE	Immunoglobulin E
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NAb	Neutralizing antibody
PCSV	Potentially clinically significant value
PD	Pharmacodynamics
PK	Pharmacokinetic

PKAS	Pharmacokinetic analysis set
POEM	Patient Oriented Eczema Measure
PT	Preferred term
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
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 software
SC	Subcutaneous
SCORAD	SCORing atopic dermatitis
SD	Standard deviation
SE	Standard error
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to pre-specify the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R3500-AD-1805 study.

1.1. Background/Rationale

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. 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. 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.

For patients with moderate-to-severe AD, topical therapies have limited efficacy, and systemic treatments are associated with substantial toxic effects.

Interleukin-33 is released by damaged epithelial tissue cells in response to insults such as allergens, viruses, or injuries. Interleukin-33 signaling activates multiple downstream inflammatory pathways, resulting in effects characteristic of both Type 1 and Type 2 inflammation. Experimental evidence suggest a role for IL-33 in pathogenesis of AD.

REGN3500 (also referred to as SAR440340) is a human $IgG4^P$ mAb that binds IL-33 with subnanomolar affinity and thereby inhibits IL-33 signaling. Preclinical murine lung models suggest that treatment with REGN3500 and dupilumab display additive effects, further suppressing pathways associated with allergic inflammation or target pathways not affected by either monotherapy. These additive effects suggest that REGN3500 plus dupilumab combination treatment may provide additional benefits in patients with AD. REGN3500 has been studied in 3 phase 1 clinical studies evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of REGN3500 in healthy volunteers and in patients with asthma, as well as in phase 2 studies in patients with AD, asthma, and COPD, alone and in combination with dupilumab

This trial is a 5-arm, placebo-controlled, double-blind, randomized, parallel-group, dose ranging (phase 2b) study over a 16-week treatment period followed by a 20-week safety follow-up period in approximately 300 adult patients with moderate-to-severe AD. The five treatment groups are:

- REGN3500 300 mg Q2W
- REGN3500 300 mg Q4W
- REGN3500 100 mg Q4W
- REGN3500 30 mg Q8W
- Placebo Q2W

The administrative looks on study R3500-AD--l798 (Efficacy and Safety of REGN3500 Monotherapy and Combination of REGN3500 Plus Dupilumab in Adult Patients With Moderate-to-Severe Atopic Dermatitis) were conducted to make strategic decisions on the clinical development program for REGN3500 by an unblinded management team not involved with the conduct of the study. The first administrative look was based on data cutoff on 18Nov2019 and the second on 24Jan2020. The data analyses indicated the lack of efficacy of REGN3500 in patients with moderate to severe atopic dermatitis when compared to placebo. Safety information currently available from this study did not suggest safety concerns related to REGN3500. As a result of lack of efficacy of REGN3500 from study R3500-AD-1798, Regeneron Pharmaceuticals, Inc and Sanofi have discontinued the REGN3500 atopic dermatitis program, and terminated the ongoing AD studies earlier than planned (R3500-AD-1798 and R3500-AD-1805). Therefore, all analyses of these 2 studies will be descriptive; no hypothesis testing will be performed. However, clinical development of REGN3500 for the treatment of other diseases remains ongoing.

1.2. Study Objectives

1.2.1. Primary Objectives

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.

1.2.2. 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 moderat-to-severe AD

1.2.3. Other 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.

1.2.4. Modifications from the Statistical Section in the Final Protocol

The current active protocol for countries other than Japan is the protocol amendment 3 and the one for Japan is the protocol amendment 2. As mentioned on Section 1.1 , due to lack of efficacy of REGN3500 in this study, Regeneron Pharmaceuticals, Inc and Sanofi have discontinued the REGN3500 atopic dermatitis program and terminated both ongoing AD studies earlier than planned (R3500-AD-1798 and R3500-AD-1805). Due to the decision, not all planned patients were enrolled in the study. For patients who were already enrolled, investigators were instructed to discontinue the study drugs and transition these patients into post- treatment follow-up period for safety assessments. As a result, a large amount of data remained uncollected as not all enrolled

patients completed all planned study visits and study procedures for the assessments of efficacy, ADA, and biomarker endpoints. Only the abbreviated clinical study report will be reported. Therefore, the following will be removed:

- the analyses using ANCOVA model for both the primary analysis and sensitivity analysis in the primary endpoint (ie, percent change in EASI score), secondary endpoints (ie, absolute change in EASI score, absolute change and percent change in pruritus NRS) and other endpoints (ie, absolute change and percent change in pain NRS and sleep quality NRS)
- the analysis using Cochran-Mantel-Haenszel test for both the primary analysis and sensitivity analysis in the binary secondary endpoints (ie, IGA score of 0 or 1, EASI-50, EASI-75, EASI-90, and improvement in pruritus NRS ≥4)
- the multiple imputation and last observation carried forward methods for the missing data imputation in efficacy endpoints
- the imputation of missing data to non-responder except that the data is set to missing due to rescue treatment
- the analyses on association between ADA and efficacy endpoints.
- the analysis on the endpoints of BSA, SCORAD, HADS, DLQI, POEM, and GISS.
- the pharmacodynamic analysis set for biomarker analysis.

One change is that the biomarkers will be analyzed based on the full analysis set.

1.2.5. Revision History for SAP Amendments

None.

2. INVESTIGATION PLAN

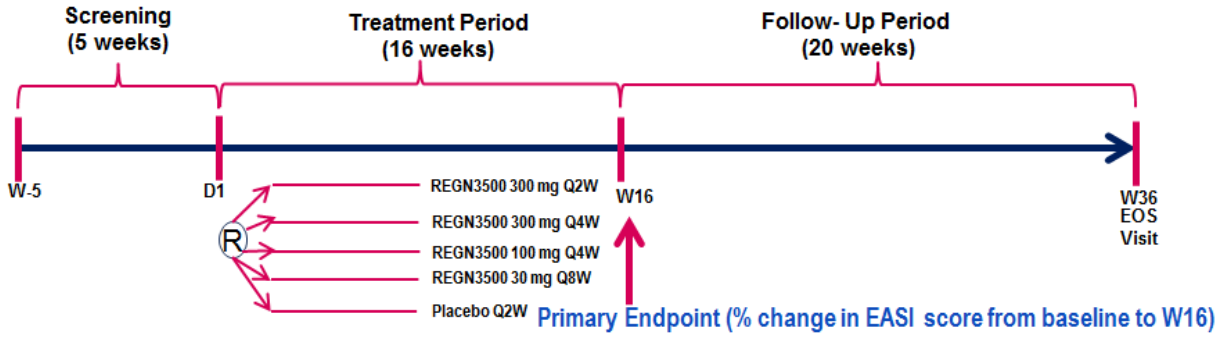
2.1. Study Design and Randomization

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. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications. 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 study duration is 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.

Approximately 300 subjects (60 subjects per treatment group) will be recruited and randomized from approximately 60 sites. Approximately 10% of patients are planned to be enrolled in Japan; and that the Japanese patients will be randomized in 2 cohorts: a sentinel cohort of 15 patients and a second cohort of 15 patients. The randomization scheme and procedure of the Japanese patients will be the same as the rest of the patients. Independent Data Monitoring Committee will review of safety data from the first 15 Japanese patients when the 15th patient completes the Day 15 visit.

Figure 1: Study Flow Diagram



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

On 12 February 2020, the Sponsor decided to stop the study. At that time, 129 subjects had been randomized including 6 Japanese patients. The sponsor instructed the investigators to transition all patients in the treatment phase to the twenty-week safety-follow-up period. These patients will stop the treatment and finish the end of treatment assessments before entering into the follow-up period. All patients who were in the screening period, but had not received study investigational medicinal product (IMP), will be screen failed for the reason of sponsor decision to discontinue study.

2.2. Sample Size and Power Considerations

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 two phase 3 dupilumab AD studies (R668-AD-1334 and R668-AD-1416).

The above calculation is for the full enrollment. However, the number of randomized patients is 129 in 5 arms including 6 Japanese patients because the Sponsors decided to stop the study prematurely due to the lack of efficacy in REGN3500 based on AD-1798 interim look data.

2.3. Study Plan

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. 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 the 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.

Patients who continue to meet eligibility criteria will undergo day 1/baseline assessments and 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 Q2WREGN3500 300 mg SC Q2W, REGN3500 300 mg SC Q4W, REGN3500 100 mg SC Q4W, REGN3500 30 mg SC Q8W, or placebo SC Q2W 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 period followed by a 20-week post-treatment follow-up period.

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. 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 determined at week 16.

Post-treatment follow-up visits will occur every 4 weeks 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 end of study (EOS) visit will occur at week 36.Efficacy will be assessed using various outcome measures of severity and extent of AD (EASI, SCORAD, IGA, GISS, BSA), patient-reported symptoms (PRO) measures of symptoms (Pruritus NRS, Pain NRS, Sleep Quality NRS, outcome Patient Oriented Eczema Measure [POEM]), mood (Hospital Anxiety and Depression Scale [HADS]), and QOL (Dermatology Life Quality Index [DLQI]).

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 ADA in serum will be collected. Serum and plasma samples will also be collected for analysis of additional biomarkers, including total IL-33, thymus and activation-regulated chemokine (CCL17; TARC), total IgE, high-sensitivity C-reactive protein (hs-CRP), and serum amyloid A (SAA). Following the initial dose of study drug administered SC on day 1, study treatment will be administered SC through week 14. The last study treatment will be administered at week 14. If medically necessary (ie, to control intolerable AD symptoms), patients may receive rescue treatment for AD (eg, systemic and topical corticosteroids) at the discretion of the investigator.

The study event table is presented in Section 10.2.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population will be used for all statistical analysis as specified below:

3.1. The Full Analysis Set (FAS)

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.

3.2. The Safety Analysis Set (SAF)

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.

The actual treatment group as treated is defined by the following rules:

- For a patient randomized to receive REGN3500, if the patient received all placebo injections, the actual treatment will be assigned as placebo.
- For a patient randomized to receive REGN3500, if the patient received at least one REGN3500 injection as planned, the actual treatment will be same as the planned treatment.
- For patients randomized to receive matching placebo for REGN3500 but accidentally received REGN3500 once injection, the actual treatment will be assigned as REGN3500.

The safety analysis will be performed separately for the treatment period, follow-up period and overall study period as defined below.

Treatment period: from the date of the first dose of study drug to the date of the end of treatment which is defined as:

- the date of Week 16 visit (or study day 113 starting from the first dose of study drug if the date of the Week 16 visit is unavailable for those patients who completed the 16 week)
- the date of early termination visit, for those patients who did not complete the Week 16 visit
- 12Feb2020 for the patients who were early terminated from the treatment per Sponsor's decision to stop the study on 12Feb2020 and Week 16 visit or early termination visit is unavailable.

Follow-up period: from the date of the end of the treatmentto the date of the end of study visit

Overall study period: from the date of the first dose of study drug to the date of the end of study visit

For the analyses of follow-up period, only a subset of SAF will be included, which is defined as the patients who entered the follow-up period and had at least one visit during the follow-up period.

3.3. Pharmacokinetic Analysis Set (PKAS)

The PK analysis set includes all randomized patients who received any study drug and who had at least one non-missing study drug concentration result following the first dose of study drug. Patients will be analyzed according to the treatment actually received.

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all patients who received any study drug and had at least 1 non-missing ADA result in REGN3500 ADA assay, after the first dose of the study drug. Patients will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The baseline value is defined as the last available value prior to the first dose of study drug, unless otherwise specified. For patients randomized but not treated, the baseline value is the last available value up to randomization.

The following demographic and baseline characteristics variables will be summarized:

- Demographic variables: Age at screening with grouping (year; ≥18-<40, ≥40-<65, ≥65-<75), sex, ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), race with grouping (White, Black, Asian, Other), region, country, baseline weight with grouping (kg, <70; ≥70-<100, ≥100), height (m), and BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30), patients with inadequate response to topicals (Yes/No) with the reasons for patients who are "No" for inadequate response to topicals.
- Baseline characteristics: Duration of AD disease with grouping (year; < median duration, ≥ median duration), Pruritus numerical rating scale (NRS) for maximum or average itch intensity, Pruritus categorical scale, Investigator's Global Assessment (IGA) score, Eczema Area and Severity Index (EASI) score, SCORing Atopic Dermatitis (SCORAD) score, Body Surface Area (BSA) Involvement of Atopic Dermatitis, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Global Individual Signs Score (GISS), Hospital Anxiety and Depression Scale (HADS), history of eye/conjuntivial discorder (such as conjunctivitis, blepharitis or keratitis), and findings of ophthalmogical exam at Baseline.

4.2. Medical History

Medical history will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the coding CRO. Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy, hives and other allergies due to medications, animals, plants, mold, etc. will be collected.

4.3. Prior / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary at the coding CRO. Patients will be counted once in all ATC categories linked to the medication.

Procedures will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO.

Prior medications/procedures: medications taken or procedures performed prior to the first dose of study drug.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit.

The prior systemic corticosteroid, immunosuppresent, phototherapy use and concomitant topical steroid eye drops or cyclosporine eye drops will be adjudicated by the clinical study director and the adjudication procedure will be documented before database lock.

4.4. Rescue Medication/or Prohibited Medication During Study

Prohibited concomitant medications: Treatment with the following concomitant medications is prohibited during the study:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than REGN3500)
- Treatment with immunomodulating biologics
- Treatment with systemic nonsteroidal immunosuppressant (may be used as rescue)
- Treatment with systemic corticosteroids (may be used as rescue)
- Treatment with TCS or TCI (may be used as rescue in which study drug will not be discontinued)
- Treatment with topical crisabarole (may be used as rescue in which study drug will not be discontinued)
- Initiation of treatment of AD with prescription moisturizers

Prohibited concomitant procedures: The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy (UVA, UVB, nbUVB, high dose UVA and PUVA)
- Tanning in a bed/booth

Rescue treatments (both medications and procedures): If medically necessary (ie, to control intolerable AD symptoms), study patients may receive rescue treatment for AD at the discretion of the investigator. 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 drug treatment.

Unless permanently discontinued from the study or discontinued from study due to sponsor's decision of stopping 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.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure. The rescue treatments will be adjudicated by the clinical study director and the adjudication procedure will be documented.

4.5. Efficacy Variable

All endpoints will be collected at time points according to Table 1.

4.5.1. Primary Efficacy Variable

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

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin, 2001). The EASI score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights. For patients of age >=8 years, the weights are 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. For patients of age <8 years, the weights are 20% = head, 20% = upper extremities, 30% = trunk, 30% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section.

4.5.2. Secondary Efficacy Variables

The secondary efficacy variables include:

- Proportion of patients achieving EASI-50 (≥50% improvement from baseline) at week 16
- Proportion of patients achieving EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients achieving EASI-90 (≥50% improvement from baseline) at week 16
- Absolute change in EASI score 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

Investigator's Global Assessment (IGA)

The IGA is a static 5-point assessment instrument to rate AD disease severity globally in clinical studies. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration.

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) using an electronic questionnaire (e-diary).

At screening, patients will be instructed on using the e-diary to record the worst intensity of their itch/pruritus, using a scale from 0 to 10, where 0 is no itch and 10 is the worst itch imaginable. Patients will complete the rating scale twice every day, morning and evening reports, 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.

The daily peak pruritus NRS score is the worse one between the morning and evening scores of the day.

The baseline Pruritus NRS score will be determined based on the average of daily NRS scores during the 7 days immediately preceding randomization (i.e. study day -7 to day -1). A minimum of 4 daily scores out the 7 days is required to calculate the baseline average score.

For post-baseline Pruritus NRS score, the weekly average is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

The weekly worst score is calculated by taking the worst score within the week.

The endpoint "Proportion of patients with improvement (reduction) of peak daily Pruritus NRS ≥4 from baseline to week 16" will be based on the weekly average of daily peak Pruritus NRS score.

Body Surface Area (BSA) Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each 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 the sum of all the percentages combined. .

4.5.3. Other Efficacy Variables

Other efficacy variables include:

- Change (absolute and percent) from baseline to week 16 in weekly average of daily Peak Pain NRS
- Change (absolute and percent) from baseline to week 16 in weekly average of daily Sleep Quality NRS

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 to answer 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).

The daily peak pain NRS score and weely average for post-baseline pain NRS score are calculated using the same algorithm for daily peak, and weekly average of pruritus NRS score.

Sleeping 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:

"Select the number that best describes the quality of 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).

The baseline sleeping quality NRS score will be determined based on the average of daily NRS scores during the 7 days immediately preceding randomization (i.e. study day -7 to day -1). A minimum of 4 daily scores out the 7 days is required to calculate the baseline average score.

For post-baseline sleeping quality NRS score, the weekly average is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)", "High Level Term (HLT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA) latest version available.

An **Adverse Event** 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.

AEs also include: any worsening (i.e. 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; abnormal laboratory findings considered by the investigator to be clinically significant; and any untoward medical occurrence.

The criteria for determining whether an abnormal laboratory, vital sign or ECG finding should be reported as an AE are as follows:

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

A **Serious Adverse Event** is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

The pre-treatment AEs are AEs that developed or worsened in severity during pre-treatment period defined as the period from the patient providing informed consent upto the first dose of study drug.

Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment emergent period defined as the period from the administration of first study dose to the EOS visit. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

The skin infection TEAEs will be identified based on blinded adjudication of all reported TEAEs under the two primary system organ classes (SOCs): SOC = “Infection and infestations” or SOC = “Skin and subcutaneous tissue disorders”. Blinded adjudication will be done and finalized by the study medical monitor before database lock.

4.6.2. Adverse Events of Special Interest

In this study, the adverse event of special interest (AESI) category includes:

- 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
- 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)

- Significant ALT elevation

a. ALT >3×ULN associated with total bilirubin >2×ULN; or
b. ALT >5×ULN in patients with baseline ALT ≤2×ULN; or
c. ALT >8×ULN if baseline ALT >2×ULN

The search criteria for AESIs are provided in Section 10.4.

4.6.3. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory.

Samples for laboratory testing will be collected according to visit schedule (Table 1). Tests will include

Serum Chemistry

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

Other Laboratory Tests

Serum and urine pregnancy testing will be performed for all female patients of childbearing potential at time points according to Table 1. The following tests will be performed at screening: HIV, HBsAg, HBsAb, HBcAb, hepatitis C antibody, and tuberculosis.

4.6.4. Vital Signs

The following vital signs parameters will be collected:

- Respiratory rate (bpm)
- Pulse (beats/min)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (°C)

Vital signs (sitting blood pressure, pulse, and respiration rate) will be collected predose and 30 (±10) minutes postdose. In addition, body temperature should be taken predose. See Table 1 for assessment time points.

4.6.5. 12-Lead Electrocardiography (ECG)

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] = $QT/[RR^{0.33}]$ and QTc Bazett [QTcB]=$QT/[RR^{0.5}]$), ECG status: normal, abnormal not clinical significant or abnormal clinical significant. See Table 1 for assessment time points.

4.6.6. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal. A thorough and complete physical examination will be performed at time points according to visit schedule (Table 1).

Any abnormal findings during the screening period are recorded as medical history. Any abnormal findings during post-screening period are recorded as adverse events.

4.6.7. Other Safety Variables

Body weight and height will be measured at time points according to Table 1.

Ophthalmological exams: 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 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.

4.7. Pharmacokinetic Variables

Samples for measurement of functional REGN3500 or total IL-33 (REGN3500 target) will be collected at visits listed in Table 1.

4.8. Immunogenicity Variables

The immunogenicity variables are anti-drug antibody (ADA) status and titer at each time-point/visit. Serum samples for anti-REGN3500 antibody bioanalysis will be collected at time points according to visit schedule (Table 1). 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.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA responses and titer categories are defined as follows:

- ADA Negative, defined as ADA negative response in the REGN3500 ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold for anti-REGN3500 antibody assay over baseline titer levels
- Treatment-emergent response, defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient
  - Persistent Response - Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by at least 16-week period, for anti-REGN3500 antibody assays, with no ADA negative samples in between
  - Indeterminate Response - as a treatment-emergent response with only the last collected sample positive in the ADA assay
  - Transient Response - a treatment emergent ADA positive assay response that is not considered persistent or indeterminate.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold for anti-REGN3500 antibody assay over baseline titer levels, when baseline results are positive
- Titer categories (Maximum titer values)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

4.9. Pharmacodynamic and Biomarker Variables

Biomarkers to be analyzed in this study are:

- TARC
- Total serum IgE
- hsCRP
- Serum amyloid A (SAA)
- Lactate dehydrogenase (LDH) [which will be measured as part of the blood chemistry]

Serum samples for measurements of biomarkers to study the PD activity of study treatments in AD patients will be collected at time points according to Table 1.

5. STATISTICAL METHODS

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

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

All data will be summarized by treatment group.

The safety data collected during the COVID-19 pandemic will be analyzed separately for the impacted patients, if applicable.

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics variables (see Section 4.1) will be summarized by treatment group for FAS. Listing of demographics and baseline characteristics will be presented.

5.2. Medical and AD History

Medical history will be summarized by primary SOC and PT for each treatment group for SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups. Medical history will be listed.

Information on conditions related to AD includes diagnosis of AD and AD treatment history, asthma, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyps, eosinophilic esophagitis, food allergy hives and other allergies due to medications, animals, plants, mold, etc History of eye/conjuntivial discorder will also be summarized.

5.3. Prior/concomitant Medications and Procedures

Number and proportion of patients taking prior/concomitant medications will be summarized by treatment group for SAF, sorted by decreasing frequency of ATC Level 2 and ATC level 4 based on the incidence in the REGN3500 treatment group. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication. The prior systemic corticosteroid, immunosuppresent, phototherapy use and the concomitant topical steroid eye drops or cyclosporine eye drops will be summarized similarly.

Number and proportion of patients undergoing a prior/concomitant procedure(s) will be summarized, sorted by decreasing frequency of SOC and PT based on the incidence in the REGN3500 treatment group. Patients will be counted only once for each SOC and PT linked to the procedure.

The compliance of moisturizers (emollients) used from 7 days before the baseline visit to end of study, which is defined as the (number of days moisturizers used during the period) / (number of days within the period) x 100%, will be summarized by treatment group.

Descriptive statistics or listings will be provided for the prior and concomitant medications and procedures for the patients impacted by COVID-19 pandemic as well as for three periods (pre-, during-, post-COVID-19 periods), if applicable.

5.4. Rescue/Prohibited Medications and Procedures

Rescue/prohibited medication and procedures will be summarized by treatment group for SAF and FAS, separately. Number and proportion of patients taking medications and rescue medications will be summarized, sorted by decreasing frequency of ATC level 2 and ATC level 4 based on the incidence in the REGN3500 treatment group. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

Number and proportion of patients undergoing prohibited procedures and rescue procedures will be summarized, sorted by decreasing frequency of SOC and PT based on the incidence in the REGN3500 treatment group. Patients will be counted only once for each SOC and PT linked to the procedure.

Prohibited medications will be listed.

Descriptive statistics or listings will be provided for the rescue medications for the patients impacted by COVID-19 pandemic as well as for three periods (pre-, during-, post-COVID-19 periods), if applicable.

5.5. Subject Disposition

The following summaries will be provided:

- The total number of screened patients
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set by visit and overall
- The total numbers of patients who completed the study treatment and who discontinued the study treatment with the reason of discontinuation
- The total numbers of patients who completed the study and who discontinued the study with the reason of discontinuation (including COVID-19 related reasons)
- The total number of patients who entered follow-up period

The following listings will be provided:

- Listing of patient disposition including: date of randomization, date of the last visit, received dose, completed study treatment or discontinued, completed study or discontinued
- A listing of patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from the treatment or from the study, along with reasons for discontinuation
- A summary table and a listing of protocol deviations will be provided.
- The listing of the protocol deviations for the prohibited treatments will be provided.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Compliance with study treatment will be calculated for REGN3500 injection by treatment group as follows:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections taken during exposure period) x 100%

Summary of study drug administration will include the number of study drug doses administered and treatment compliance. The treatment compliance will be presented by the following specific ranges for each treatment group: <80%, and ≥80%.

Listing of dose administration: including date/time, study day, number of injections, locations of injections, dosing information, and whether or not the total dose is administered for each dose will be presented.

5.6.2. Treatment Exposure and Observation Period

The duration of treatment exposure during the study in days is calculated as:

(Date of last study drug injection – date of first study drug injection) + x days , where x days are 7, 14, 28, 56 days for QW, Q2W, Q4W, and Q8W, respectively.

The calculations are regardless of temporary dosing interruption. The duration of exposure during the study will be summarized by treatment group using number of patients, means, SD, minimums, Q1, medians, Q3 and maximums.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well: ≥ 15 days, ≥ 29 days, ≥ 43 days, ≥ 57 days, ≥ 71 days, ≥ 85 days, ≥ 99 days, and ≥ 113 days.

The duration of observation period during the study in days is calculated as:

(Date of the last visit – date of the first study drug injection) +1.

The number (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as: < 15 days, ≥ 15 days, ≥ 29 days, ≥43 days, ≥ 57 days, ≥ 71 days, ≥ 85 days, ≥99 days, ≥113 days, ≥141 days, ≥169 days, ≥197 days, ≥225 days and ≥253 days. Since the Sponsor stopped the study, it is possible that no patient reaches some time categories.If so, these categories will not be reported.

5.7. Analyses of Efficacy Variables

All efficacy variables will be summarized by descriptive statistics by treatment groups and visits during the treatment period.

The analyses of efficacy variables are described in subsections below and summarized in Section 10.1.

Since the Sponsor stopped the study prematurely, many patients did not reach week 16 when the study was terminated. The last assessments of such patients will be re-mapped to the next scheduled visits in general. Details have been documented in Section 6.4.

5.7.1. Analysis of Primary Efficacy Variable

The primary efficacy variable, the percent change in EASI score from baseline to week 16, will be summarized by treatment groups and visits using descriptive statistics. The results will be tabulated based on the following cases.

1. Observed values regardless of rescue treatment use
2. Observed values and the data will be censored after the rescue treatment is used

The primary efficacy data, regardless of whether the patient remains on study treatment or discontinues the study treatment but remains in the study, will be used for analysis. Specifically, if a patient stays in the study until the end of the study planned placebo-controlled treatment period, all efficacy data collected up to the study planned end of treatment visit will be included in the primary analysis, regardless of whether the patient is on treatment or not.

5.7.2. Analysis of Secondary Efficacy Variables

All secondary endpoints will be evaluated on the FAS.

The binary secondary efficacy endpoints will be analyzed using descriptive statistics by treatment groups and visits. The results will be tabulated based on the following cases.

1. Observed values regardless of rescue treatment use.
2. Observed values and the data will be censored after the rescue treatment is used. Patients with missing value due to rescue treatment will be counted as non-responder .

The continuous secondary efficacy variables will be analyzed using the same approach as that used for the analysis of the primary endpoint.

Similar to the primary endpoint, the secondary efficacy data, regardless of whether the patient remains on study treatment or discontinues the study treatment but remains in the study, will be used for analysis.

5.7.3. Adjustment for Multiple Comparison

There will be no control for multiplicity for this study.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF and presented for each treatment group.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.3.

The summary of safety results will be presented for each treatment group.

Descriptive statistics or listings will be provided for the safety endpoints for the patients impacted by COVID-19 pandemic as well as for three periods (pre-, during-, post-COVID-19 periods), if applicable.

5.8.1. Adverse Events

Listing of TEAEs, serious TEAEs, and TEAEs resulting in death and study drug discontinuation will be generated.

Numbers and proportions of patients reporting TEAEs will be summarized for treatment period and follow-up period, sorted by alphabetical order of SOC and decreasing frequency of PT based on the incidence in the REGN3500 treatment group.

Summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT
  - TEAEs by PT
  - Common TEAEs by SOC/PT (incidence with PT ≥5%)
  - TEAEs related to study drug as assessed by the investigator by SOC/PT
  - TEAEs related to study procedure as assessed by the investigator by SOC/PT
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs related to study drug as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study procedure as assessed by the investigator by SOC/PT
  - Common non-serious TEAEs by SOC/PT (incidence with PT ≥5%)
  - TEAE per 100 patient years by SOC/PT during treatmen period only
- Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study drug as assessed by the investigator by SOC/PT
  - Serious TEAEs related to study drug as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation from study treatment by SOC/PT
- Serious TEAE per 100 patient years by SOC/PT during treatmen period only
- Death by SOC/PT

- Skin infection TEAEs by SOC and PT

5.8.2. Analysis of Adverse Events of Special Interest

The adverse events of special interest (AESI) will be summarized by AESI category (see Section 10.4) and by high level term and PT.

5.8.3. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables for overall study period, treatment period and follow-up period will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- Descritive statistics of blood eosinophils and change and percent change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs for patients without PCSVs in corresponding category at baseline
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by patient and visit will be provided.

5.8.4. Analysis of Vital Signs

Summaries of vital sign variables for the overall study period, treatment period and follow-up period will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSV
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs for patients without PCSVs in corresponding category at baseline
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings of vital sign will be provided with flags indicating the treatment-emergent PCSVs.

5.8.5. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by the overall study period, treatment group for treatment period and follow-up period will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs for patients without PCSVs at baseline in corresponding category
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings of ECG will be provided with flags indicating PCSVs.

5.8.6. Physical Exams

The number (n) and percentage (%) of patients with abnormal physical exams will be summarized at baseline, end of treatment period and end of study by treatment group.

5.8.7. Ophthalmological exams

The findings from the ophthalmological exams will be summarized and listed.

5.9. Analysis of Pharmacokinetic Data

No formal statistical analysis will be performed. Concentrations of functional REGN3500 and total IL-33 (REGN3500 target) in serum will be summarized at each time point by treatment group 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.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics in the ADA analysis set.

The following analysis will be provided based on AAS:

- Number (n) and percent (%) of ADA-negative patients (pre-exisiting immunoreactivity and ADA negative at all timepoints) in the respective ADA assay by treatment groups
- Number (n) and percent (%) of ADA positive patients (treatment-emergent and treatment-boosted responses) by treatment groups and ADA titer categories
- Number (n) and percent (%) of treatment-emergent ADA-positive patients by treatment group and ADA titer categories

a. Number (n) and percent (%) of persistent treatment-emergent ADA-positive patients
b. Number (n) and percent (%) of indeterminate treatment-emergent ADA-positive patients

c. Number (n) and percent (%) of transient treatment-emergent ADA-positive patients

- Number (n) and percent (%) of treatment-boosted ADA-positive patients by treatment groups and ADA titer categories
- Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA responses

5.11. Association of Immunogenicity with Exposure & Safety

5.11.1. Immunogenicity and Exposure

Potential association between ADA variables and systemic exposure to study treatment (REGN3500) will be explored by treatment group. Plots of study drug concentration may be provided for analyzing the potential impact of ADA response status and titer on corresponding drug concentration.

5.11.2. Immunogenicity and Safety

Association between ADA and safety event may be explored with a primary focus on the following events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

The above mentioned safety analyses will be conducted using the following ADA response categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response,
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
- Patients with persistent treatment-emergent ADA response
- Maximum post-baseline titer level in treatment emergent or treatment boosted ADA positive patients:
  - Low (titer < 1,000)
  - Moderate (1.000 ≤ titer ≤10,000)
  - High (titer > 10,000)

5.12. Analysis of Biomarker Data

Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the following biomarker variables based on FAS analysis set:

- TARC
- total serum IgE
- hsCRP
- Serum amyloid A (SAA)
- Lactate dehydrogenase (LDH)

Serum total IgE and LDH are established clinical assays; the upper limit of normal (ULN) from the central lab reference range will determine the threshold for normal vs. elevated status.

Summary tables with normal/elevated status for serum total IgE and LDH at baseline and each post-baseline visit (until end-of-study) will be provided by treatment group.

6. DATA CONVENTIONS

The analysis conventions that are described in this section will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the first administration of study drug.

If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The baseline of worst itch scale is defined in Section 4.5.2.

The following rules specify the determination of baseline by both date/time information:

- For the AE, lab, PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
- For other data except AE, lab, PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen-failure subject ID or enrolled subject ID.

6.2. General Data Handling Convention

For the laboratory safety variables data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is ‘D’.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D'.

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before inform consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However in order to simplify the programming flow, the imputation is proposed to in line with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date - 1 instead. Imputation flag is 'M'.

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use end of follow up date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of follow up date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of follow up date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Visit Windows

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described in the study protocol and SAP "Schedule of Events". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits and early termination (ET) visit have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled visits:

Visit	Target Day	Analysis Time Window Based on Study Day*
Screening	<1	<1
Baseline	1	1
Week 2	15	[2, 21]
Week 4	29	[22, 36]
Week 6	43	[37, 50]
Week 8	57	[51, 64]
Week 10	71	[65, 78]
Week 12	85	[79, 92]
Week 14	99	[93, 106]
Week 16	113	[107, 127]
		Analysis Time Window Based on Days Relative to Treatment Period End Date**
Week 20	28	[1, 42]
Week 24	56	[43, 70]
Week 28	84	[71, 98]
Week 32	112	[99, 126]
Week 36	140	>=127

*study day is calculated relative to the date of first study drug injection.
** Days relative to treatment period end date =visit date –the treatment period end date.

If the early termination (ET) occurs during the treatment period, it will be mapped to next scheduled visit during the period. Similarly, it occurs during the follow-up period, it will be mapped to the next scheduled visit during the follow-up period:

For patients who discontinued from the treatment due to the sponsor's decision to stop study, the Week 16 will be mapped to the patients' next scheduled visit.

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ET are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

For the daily collected ePRO data, the analysis visit windows will be implemented following the procedure below:

Step 1: Derive the study day or days relative to the treatment period end date,

If diary date ≥ 1st injection date and ≤ the treatment period end date, then diary study day=diary date – 1st injection date +1.

If diary date < 1st injection date, diary study day=diary date – 1st injection date.

If diary date > the treatment period end date, days relative to treatment period end date = diary date -treatment period end date.

Step 2: Windows for treatment period are defined as diary study day -7 to -1 = BL, 1 to 7 = week 1, 8 to 14 = week 2, etc, with 7 days interval between visit windows. Similarly, windows for follow-up period are defined as days relative to treatment period end date 1 to 7 = week 17, 8 to 14 = week 18, etc, with 7 days interval between visit windows.

7. INTERIM ANALYSIS

No interim with alpha spending is planned.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

9. REFERENCES

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber Ml. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10(1):11-8.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Parameter(s)	Endpoints	Primary Statistical Method	Supportive/Sensitivity Statistical Method	Subgroup Analysis
Eczema Area and Severity Index (EASI)	• % change from baseline • Change from baseline • EASI 75 • EASI 50 • EASI 90	Descriptive Statistics	No	No
Investigator's Global Assessment (IGA)	IGA 0 to 1 responder	Descriptive Statistics	No	No
Weekly average of daily peak Pruritus NRS	• Percent change and absolute change from baseline • Proportion with ≥4 improvement from baseline	Descriptive Statistics	No	No
Weekly average of daily Pain NRS	Percent change and absolute change from baseline	Descriptive Statistics	No	No
Weekly average of daily Sleep Quality NRS	Percent change and absolute change from baseline	Descriptive Statistics	No	No

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Time and Events

Table 1: 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		Urine		Urine		Serum	Urine	Urine	Urine	Urine	Serum	Urine	Serum
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

	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	-	-
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
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.

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 in the protocol amendment 3). 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. Japanese sentinel cohort has Day 2, 4, and 8 PK sample collections.
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 1.
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 in the protocol amendment 3).
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 in the protocol amendment 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.

10.3. Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV) for REGN3500 AD studies in Adults

Parameter	Treatment Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in μmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin ≤1.5 ULN) at baseline	Conjugated bilirubin dosed on a case-by-case basis.

Parameter	Treatment Emergent PCSV	Comments
(ALT or AST) and Total Bilirubin	((ALT>3 ULN or AST>3 ULN) and TBILI>2 ULN) and baseline ((ALT <=3 ULN and AST<=3 ULN) **or** TBILI <=2 ULN)	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria
Chloride Hypochloremia Hyperchloremia	 <80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	Two independent criteria
Sodium Hyponatremia Hypernatremia	 ≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria

Parameter	Treatment Emergent PCSV	Comments
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Threshold for therapeutic intervention.
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia		
	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
Albumin	≤25 g/L and >25 g/L at baseline	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black)	Increase in WBC: not relevant.
	≥16.0 Giga/L and < 16 Giga/L at baseline	To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline for all races	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.

Parameter	Treatment Emergent PCSV	Comments
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female.	Three criteria are independent.
	≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
Pulse	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.

Parameter	Treatment Emergent PCSV	Comments
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula. *QTc prolonged and ΔQTc>60 ms are the PCSV to be identified in individual subject/patient listings. 5 independent criteria

10.4. Search Criteria for TEAE of Special Interest

The search criteria are meant to assist the process of identification of TEAE of Special Interest. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases. Hence an additional blinded review of all PTs in the database may be performed by the Medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE that may have been inaccurately assigned as AESI by the algorithmic search.

AESI	**Search Criteria**
Anaphylactic reactions	For SMQ "anaphylactic reaction" An **algorithmic approach** will be used. A case must include either: 1. A narrow term (a term from Category **A**); 2. Patient with both a term from Category **B** AND a term from Category **C**; 3. Patient with a term from Category **D** AND { a term from Category **B** - OR a term from Category **C** } For bullets 2 and 3, the search terms that are included under the SMQ for a particular event need to have the same start date (for e.g. if search shows cough (category B term) occurring at day 3 and urticaria (category C term) occurring at day 7, this event is not adjudicated as anaphylactic reaction as this is inconsistent with the clinical presentation of anaphylaxis as an acute event with simultaneous involvement of 2 or more body systems. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
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)	broad CMQ conjunctivitis (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Ocular hyperaemia, Conjunctival hyperaemia, Xerophthalmia) Blepharitis PTs (Blepharitis, blepharitis allergic) **AND** Serious AE= "Yes" OR Severity= "severe" OR lasting ≥4 weeks

	Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Keratitis	Any of the following PTs: • Keratitis • Allergic keratitis • Ulcerative keratitis • Atopic keratoconjunctivitis • Herpes ophthalmic • Ophthalmic herpes simplex Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Severe ISRs that last longer than 24 hours	- HLT = Injection site reactions - Severity = "severe" or Serious AE ="Yes" - AE duration ≥1 day
Mycosis fungoides or other forms of cutaneous T-cell lymphoma	-HLT = Mycoses fungoides -OR LLT = Sezary syndrome -OR LLT = Cutaneous T-cell lymphoma -OR PT = Cutaneous T-cell dyscrasia
Any severe infection	-SOC = Infections and infestations -Severity = "severe" OR Serious AE= "Yes"
Any infection requiring treatment with parenteral antibiotics	SOC = Infections and infestations - Action taken for AE = "medication"

	- ConMed: ATC3= “Antiinfectives” during the TEAE course (between start and stop dates), Route = IV, IM
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	-SOC = Infections and infestations -Action taken for AE = “medication” -Check CM: ATC3=” BETA-LACTAM ANTIBACTERIALS, PENICILLINS” OR “OTHER ANTIBACTERIALS” during the TEAE course (between start and stop dates), Route = PO and Treatment duration >14 days
Any clinical endoparasitosis	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infections
Any opportunistic infection[a] a:The definition of opportunistic infections is referring to the recent consensus guidance for opportunistic infections in the setting of biologic therapy (K L Winthrop et al, 2015)	The following HLTs plus PTs -HLT = Pneumocystis infections -HLT* = Fungal infections NEC -HLT* = Pseudallescheria infections -HLT = Herpes viral infections -HLT = Paracoccidioides infections -HLT = Sporothrix infections -HLT = Cryptosporidia infections -HLT* = Trypanosomal infections -HLT* = Campylobacter infections -HLT* = Shigella infections -HLT* = Vibrio infections Plus the following PTs -Polyomavirus-associated nephropathy -BK virus infection -Cytomegalovirus infection -Post transplant lymphoproliferative disorder -Progressive multifocal leukoencephalopathy -*Bartonellosis -Blastomycosis -Toxoplasmosis

	-Coccidioidomycosis -Histoplasmosis -*Aspergillus infection -Systemic candida -Oropharyngeal candidiasis -Cryptococcosis -Listeriosis -Tuberculosis -Nocardiosis -Mycobacterial infection -*Salmonellosis -*Hepatitis B -Herpes zoster -*Strongyloidiasis -Microsporidia infection -Visceral leishmaniasis -*Hepatitis C *Note: *Blinded manual adjudication of relevant PTs under each of HLTs listed above will be required by the study medical monitor, before database locks*
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	Algorithm is to first search adverse event PT term = "Alanine aminotransferase increased" and the event must meet the following: ALT>3*ULN associated with total bilirubin>2*ULN or ALT>5*ULN with baseline ALT≤2*ULN or ALT>8*ULN if baseline ALT>2*ULN

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