STATISTICAL ANALYSIS PLAN
VERSION: AMENDMENT 1

Clinical Study Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study in Cat-Allergic Patients with Allergic Rhinitis Who Live with a Cat to Assess the Efficacy and Safety of Anti-Fel d 1 Antibodies during Natural Cat Exposure in the Home

Compound:	REGN1908-1909
Protocol Number:	R1908-1909-ALG-2102
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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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

ACQ-5	Asthma Control Questionnaire 5 Question Version
ADA	Anti-drug antibody
ADSD	Asthma Daytime Symptom Diary
ADSS	Asthma Daily Symptom Score
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANSD	Asthma Nighttime Symptom Diary
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CSMS	Combined symptom and medication score
DMS	Daily medication score
Df	Dermatophagoides farina
Dp	Dermatophagoides pteronyssinus
EAR	Early asthmatic response
ECG	Electrocardiogram
EEU	Environmental exposure unit
FAS	Full analysis set
FDA	United States Food and Drug Administration
Fel d 1	*Felis domesticus* allergen 1
GINA	Global Imitative for Asthma
HDM	House dust mite
HRQoL	Health related quality of life
IA	Interim analysis
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E

INCS	Intranasal corticosteroids
mAb	Monoclonal antibody
MWD	Mean wheal diameter
NAb	Neutralizing antibody
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire for Ages 12+
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SIT	Specific immunotherapy
SOC	System organ class
SPT	Skin prick test
TEAE	Treatment-emergent adverse event
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
TSS	Total symptom score
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to any 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 from the R1908-1909-ALG-2102 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to data lock and before code breaking.

1.1. Background and Rationale

Cat allergens are among the most important indoor allergens and a common cause of IgE-mediated allergic disease worldwide, affecting approximately 26% of patients consulting for suspected allergy to inhalant allergens in Europe. Approximately 12% to 15% of the United States (US) population has a known sensitivity to cat allergen . About 25% to 34% of households in Europe and the US reported owning a cat in the home.

Felis domesticus allergen 1 (Fel d 1) is produced by the skin and by salivary and lacrimal glands of the cat. Dried saliva and dandruff are spread from the cat hair as small airborne particles into the surrounding environment that readily adhere to surfaces such as walls, carpets, and furniture. About 90% to 95% of cat allergic individuals are sensitized to Fel d 1, which is the immunodominant allergen. While the highest amount of Fel d 1 allergen is found in households with cats and the concentration correlates with the number of cats kept in a home, this allergen can also be carried on clothes and shoes into homes and schools without cats and may persist in these areas for months to years.

Nasal and ocular symptoms are the most frequently reported cat allergy symptoms; although nasal symptoms are often considered most bothersome, ocular symptoms commonly occur with rhinitis. Treatment of cat allergy includes a recommendation for removal of the cat from the home. Despite this recommendation, often patients continue to live with their cat(s) due to emotional attachment. Rhinoconjunctivitis is treated with antihistamines and intranasal corticosteroids (INCS), which are only moderately effective for nasal symptoms. The best reported treatment effects for antihistamines and INCS are 5% to 11% relative reduction of total nasal symptoms compared to placebo. Allergic conjunctivitis symptoms are typically treated with topical antihistamines that are sometimes combined with mast cell stabilizers .

The association between cat allergy and asthma is significant. Approximately 30% of allergic asthmatics reportedly have a concomitant allergy to cats. More than 50% of cat-sensitized patients have a diagnosis of co-morbid asthma, ranging from intermittent mild to potentially life-threatening asthmatic exacerbations requiring treatment with short- and long-acting bronchodilators, inhaled corticosteroids, and broader immune-targeting agents.

Specific immunotherapy (SIT) is a disease-modifying, standard-of-care treatment option for patients with allergic rhinoconjunctivitis triggered by cat allergen when pharmacological therapies are insufficient. Allergen-specific polyclonal IgG4 titers increase during SIT and may inhibit effector cell activation by blocking binding of IgE-allergen complex to high-affinity IgE receptors

on mast cell and basophil surfaces, thereby effectively preventing early phase allergic symptoms . Although SIT can provide long-lasting protection from allergic disease, SIT carries a risk of local and systemic adverse reactions (especially in uncontrolled or severe asthma), is variably effective among different patients, and can take 3 to 5 years to induce permanent immune tolerance.

REGN1908 and REGN1909 are human IgG4 monoclonal antibodies (mAbs), which bind independently, non-competitively, and with high affinity to the Fel d 1 allergen and are being developed as an antibody cocktail (REGN1908-1909) for the treatment of allergic disease triggered by exposure to cats or cat hair. Fel d 1 is the major cat allergen which is recognized in more than 90% of cat-allergic patients and accounts for 60% to 90% of the total allergenic activity in cat dander .

In a phase 1b proof-of-mechanism (POM) study (R1908-1909-ALG-1325), a single 600 mg subcutaneous (SC) dose of REGN1908-1909 (300 mg each of REGN1908 and REGN1909) prophylactically blocked the early allergic response to nasal challenge with cat allergen and resulted in a 29% improvement in total nasal symptom score (TNSS) following a nasal challenge 8 days after REGN1908-1909 administration (which was the earliest time point assessed), compared with placebo. REGN1908-1909 treatment reduced TNSS AUC (0 to 1 h) by 56%, 61%, 51%, and 51% on days 8, 29, 57, and 85 respectively; resulting in 29%, 33%, 14%, and 23% reduction vs placebo and achieving nominal statistical significance vs placebo at every time point except day 57 (ANCOVA, $p = 0.0005$, 0.0004, 0.1321, 0.0187, respectively).

In a phase 2 trial in cat allergic patients with Global Initiative for Asthma (GINA) I asthma, (R1908-1909-ALG-1703), a single 600 mg SC dose of REGN1908-1909 (300 mg each of REGN1908 and REGN1909) prophylactically blocked the early asthmatic response (EAR) in an Environmental Exposure Unit (EEU) as early as day 8 and through day 85 (the last time point evaluated). Compared with placebo, REGN1908-1909 significantly increased the median time to EAR from 51 minutes (baseline) to >4 hours on days 8 (hazard ratio [HR]=0.36; $p < 0.0083$), 29 (HR = 0.24; $p < 0.0001$), and 85 (HR = 0.27; $p = 0.0003$), and to 232 mins on day 57 (HR = 0.45; $p = 0.0222$). As compared to placebo, an approximately 3-fold higher cumulative allergen quantity was tolerated relative to baseline after single-dose REGN1908-1909 at days 8 ($p = 0.003$), 29 ($p < 0.001$), 57 ($p = 0.023$), and 85 ($p = 0.003$). Additionally, REGN1908-1909 significantly reduced skin test reactivity (mean wheal diameter) provoked by a skin prick test (SPT) with serial cat allergen titration at these same time points, suggesting that inhibition of immediate IgE-mediated responses may be a key mechanism by which REGN1908-1909 ameliorated the acute bronchoconstriction in this study.

In all studies to date (R1908-HV-1240, R1908-1909-ALG-1325, and R1908-1909-ALG-1703), REGN1908-1909 was generally well tolerated with an acceptable safety profile. There were no deaths, systemic hypersensitivity reactions, or anaphylaxis reported.

Additional background information on the study drug and development program can be found in the Investigator's Brochure and study protocol.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to determine the efficacy of REGN1908-1909, as compared to placebo, to reduce allergic rhinitis/conjunctivitis symptoms and allergy rescue medication use during natural cat exposure.

1.2.2. Secondary Objectives

The secondary objectives are:

- To assess the reduction of allergic symptoms and use of allergy rescue medications after treatment with REGN1908-1909 versus placebo, as measured by the individual components of the CSMS
- To assess health-related quality of life (HRQoL) as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S])
- To determine the efficacy of REGN1908-1909, as compared to placebo, to inhibit a wheal-and-flare response to a skin prick test with cat allergen
- To assess the durability of effect in allergic rhinitis and conjunctivitis symptom and medication scores after multiple doses of REGN1908-1909 compared to placebo given every 12 weeks (Q12W)
- To determine the efficacy following multiple doses of REGN1908-1909 compared to placebo at inhibiting a wheal-and-flare response to a skin prick test with cat allergen
- To estimate the effect of REGN1908-1909 on lung function, as compared to placebo, in patients with asthma
- To determine the efficacy of REGN1908-1909 as compared to placebo to reduce asthma symptoms in patients with asthma
- To assess whether there is a difference in asthma rescue medication use in patients with asthma who are treated with REGN1908-1909 compared to placebo
- To assess whether there is a difference in nighttime awakenings in patients with asthma treated with REGN1908-1909 compared to placebo
- To evaluate the short-term and long-term safety and tolerability of REGN1908-1909, including the incidence of hypersensitivity reactions, local injection site reactions, and asthma exacerbations
- To determine systemic exposure of total (free and antigen-bound) antibodies as measured by concentration of REGN1908 and REGN1909 in serum
- To assess the immunogenicity of REGN1908 and REGN1909

1.2.3. Exploratory Objectives

- To evaluate "well days"

Note: "Well days" are defined as days when the TSS is ≤2 without the use of anti-allergy rescue medications.

1.2.4. Modifications from the Statistical Section in the Protocol Amendment 3

- Additional intercurrent events for the loss of all cat(s) in the patient's home and significant change in cat allergen exposure during the efficacy assessment period have been added for the primary estimand of interest efficacy endpoints for the primary analysis. These details are specified in Section 5.6.1.
- The data handling for the intercurrent event of relevant prohibited medication use will utilize a composite strategy, combining observed data prior to prohibited medication use and imputation with the patient's worst score after prohibited medication use. This is outlined in Section 5.6.1.

1.2.5. Revision History for SAP Amendments

The primary purpose of this amendment is to update the intercurrent events strategy for use of prohibited medications and change in cat exposure per regulatory agency feedback. The major changes made include the following:

- Additional details were added regarding the analysis methods for the interim futility analysis in Section 7.2
- The categories of prohibited medication for the purposes of analysis have been updated in Appendix Section 10.5 Table 7, Table 8, and Table 9
- A treatment policy strategy will be used for all scenarios of changes in cat allergen exposure, other than travel away from cat for more than 6 weeks where hypothetical strategy will be used in this case
- A supplemental analysis will be performed using a treatment policy strategy for all intercurrent events

Additional minor updates that were made include the following:

- Additional details were added regarding the sample size adjustment in Appendix Section 10.6
- Editorial changes and additional details were added throughout.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 3, randomized, double-blind, parallel-group, multi-dose study in approximately 630 cat-allergic adult and adolescent patients (ages ≥12 to <18 years), where permitted, with allergic rhinitis with or without conjunctivitis and with or without asthma.

- Screening period of up to 12 weeks: Cat allergic patients living with a cat who are significantly symptomatic while using standard of care anti-allergy medications will be enrolled in the study. The study includes a screening period of up to 12 weeks to ensure sensitization, symptom and medication use requirements are met during the baseline period.
- Randomization to 1 of 2 treatment arms (1:1)
    - REGN1908-1909 600 mg Q12W (300 mg per mAb)
    - Placebo that replaces REGN1908-1909
- Study drug period (60 weeks +/- 7 days): to administer patients with R1908-1909 or placebo dose regimen every 12 weeks (Q12W) for a total of 5 administrations
- Post treatment period (12 weeks +/- 7 days): to continue to collect safety data (PK, immunogenicity, etc.) after patients have completed the study drug treatment

Efficacy will be evaluated by assessing the reduction of allergic nasal and ocular symptoms and the reduction in the use of allergy rescue medications during the initial 12 weeks and the last 12 weeks. The primary efficacy endpoint will be assessed during the last 12 weeks of treatment (weeks 48-60).

The initial 12 weeks of the treatment period are defined as the date of Visit 3 through Visit 6.

The last 12 weeks of the treatment period are defined as the date of Visit 12 through Visit 14.

The incidence and severity of TEAEs, including hypersensitivity reactions and local injection site reactions, will also be assessed throughout the study. Total drug concentration in serum and immunogenicity of REGN1908, and REGN1909 will also be measured throughout the study.

There will be a non-binding futility interim analysis (IA) in the study planned to be performed when at least 40% of randomized patients have completed the week 12 visit or discontinued before week 12.

Randomization will be stratified by IVRS based on the following:

- Age (adolescents vs adults)
- Asthma status (yes vs no)
- House dust mite (HDM) sensitivity (<0.7 kUa/L versus ≥0.7 kUa/L)

2.2. Statistical Hypothesis

For comparison of REGN1908-1909 to placebo, the following hypothesis of the primary endpoint (the average daily CSMS over the last 12 weeks of the treatment period [weeks 48 to 60]) will be tested:

- H_0: There is no difference in CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients receiving REGN1908-1909 and placebo.
- H_1: The CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), is different in patients receiving REGN1908-1909 and placebo.

The statistical hypothesis specified above can be tested on the secondary endpoints of clinical interest. The study will be declared positive if the null hypothesis for the primary efficacy endpoint for REGN1908-1909 versus placebo is rejected.

2.3. Sample Size and Power Considerations

The sample size will be approximately 315 patients per arm, for a total of 630 patients in two treatment groups. This study is powered to detect the difference between REGN1908-1909 and placebo on the primary endpoint of daily CSMS averaged over the last 12 weeks of the treatment period (weeks 48 to 60) when considering a 20% dropout rate by week 60.

A sample size of 251 patients per arm gives 90% power to detect a mean difference in daily CSMS, averaged over weeks 48-60, of 1.8 (20% reduction from placebo) between REGN1908-1909 (mean CSMS=7.3) and placebo (mean CSMS=9.1), assuming a common standard deviation in CSMS of 6.2. Assuming a 20% dropout rate (~64 per arm), the sample size is 315 per arm. A 2-sample t-test with 2-sided alpha of 0.049 was assumed (an administrative penalty of 0.001 will be taken from the significance level used at final analysis due to a planned interim analysis; details are provided in Section 7). Calculations were performed using nQuery+nTerim 4.0.

The sample size of 315 patients per arm also gives the power of 91% and 96% to detect a 20% reduction from placebo in TSS (SD=3.0 and mean in placebo=4.2) and daily TNSS (SD=2.3 and mean in placebo=3.3) averaged over the last 12 weeks (weeks 48 to 60), respectively. Details are displayed in Table 1.

Table 1: Summary of Statistical Assumptions and Power for Select Secondary Endpoints

Daily Score, Averaged over last 12 weeks	Mean		Anti-Fel d 1 vs Placebo		Power with n=315/arm*	Power with n=251/arm*
	Placebo	Anti-Fel d 1	% Reduction from Placebo	Reduction from Placebo (SD)		
TNSS	3.3	2.6	-20%	-0.7 (2.3)	96%	92%
TSS	4.2	3.4	-20%	-0.8 (3.0)	91%	84%

*: Two-sided t-test with alpha = 0.049, assuming 20% reduction from PBO

The assumptions of mean in the placebo and common standard deviation for the above endpoints are based on the house dust mite (HDM) SLIT-tablet data for combined rhinoconjunctivitis score during 8-week assessment period. A treatment difference of 20% relative to placebo is based on a previous phase 1b study (R1908-1909-ALG-1325) of the same molecules and the treatment effect observed for reduction in symptoms after a nasal allergen challenge over a 12-week period.

The sample size may be re-estimated in a blinded fashion after greater than 50% of patients have baseline data available using observed values of CSMS to determine the baseline placebo mean (SD) and assuming the same 20% difference between REGN1908-1909 versus placebo. If the re-estimated number is higher than the current estimation of 315 per arm, then the sample size may be increased. Further details are provided in Section 5.12.

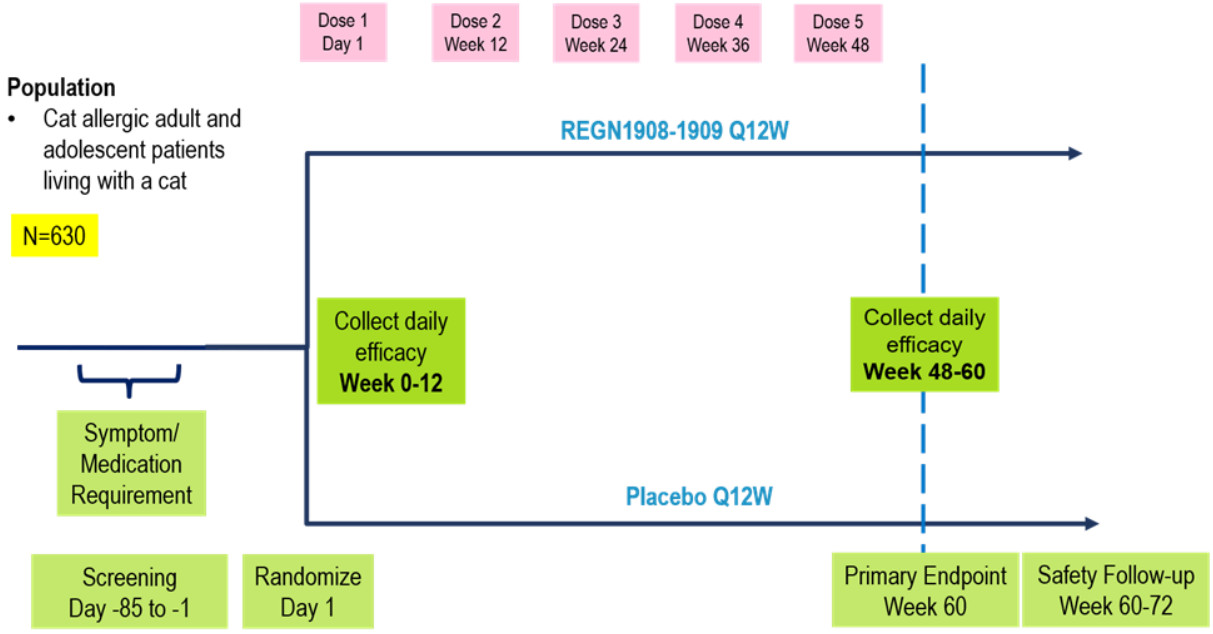
2.4. Study Plan

The total study duration is approximately 72 weeks excluding screening (Figure 1). Efficacy assessments will be done during the initial 12 weeks (weeks 0 to 12) after the first dose and during the last 12-week period (weeks 48 to 60) after last dose (dose 5) of REGN1908-1909 or placebo. For those individuals with seasonal allergies, efficacy assessments will be timed by the investigational site to ensure that the assessments are outside of any relevant pollen seasons. Approximately 630 cat-allergic subjects will be randomized 1:1 to REGN1908-1909 or placebo.

A non-binding futility interim analysis (IA) in the study is planned to be performed when at least 40% of randomized patients have completed the week 12 visit or discontinued before week 12. More details are specified in Section 7.

The Schedule of Events table is presented in Section 10.2.

Figure 1: Study Flow Diagram



3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of 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 of analysis will be used for all statistical analysis:

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 administration and all clinical safety variables will be analyzed using the SAF.

For patients randomized to either placebo or REGN1908-1909, a patient will be considered as treated with REGN1908-1909 if they received at least one dose of REGN1908-1909. If the patient receives no doses of REGN1908-1909 throughout the study, the patient will be considered as treated with placebo.

3.3. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set (PKAS) includes all patients who received any study drug and who had at least 1 non-missing concentration result following the first dose of study drug. The PK analysis set is based on the actual treatment received (as treated) rather than as randomized.

For patients randomized to either placebo or REGN1908-1909, a patient will be considered as treated with REGN1908-1909 if they received at least one dose of REGN1908-1909. If the patient receives no doses of REGN1908-1909 throughout the study, the patient will be considered as treated with placebo.

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all treated patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing ADA result following the first dose of study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis set (NAbAS) includes all treated patients (active or placebo) that are included in the ADA analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAb analysis set. Patients in the NAbAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Patients in the NAbAS that have at least one

post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

3.5. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows. The analysis for the subgroups defined may not be performed if the number of patients within the subgroup is small, e.g., <10 patients per treatment arm.

Subgroups to be considered for both efficacy and selected safety endpoints:

- Age group (≥12 to <18 years (Adolescents), ≥18 to < 65 years, ≥ 65 years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino: Yes, No)
- Race (White, Black, Asian, Other)
- Baseline cat dander IgE level (<17.5 kUa/L, ≥17.5 kUa/L)
- Asthma status (based on collected medical history: Yes, No)

Subgroups to be considered for primary and key secondary efficacy endpoints:

- House dust mite (HDM) sensitivity (Dermatophagoides farina (Df) and Dermatophagoides pteronyssinus (Dp) sIgE <0.7 kUa/L, Either Df or Dp sIgE ≥0.7 kUa/L)
- Region (Canada, United States, Europe)
- Number of cats at baseline (1, 2, > 2)
- Patient Global Impression of Severity (PGIS) at baseline (no symptoms/mild, moderate, severe)
- Prior cat immunotherapy (Yes, No)
- Baseline sensitization status based on sIgE or SPT (only sensitized to cat allergens (mono-sensitized), and those sensitized to other allergens including seasonal and perennial allergens)

Note: Cat allergens and other allergens are listed as below for SPT and sIgE:

	Cat allergens	Other allergens
SPT	Cat Hair	**Seasonal allergens:** Tree (mix) Grass (mix) Ragweed **Perennial allergens:** House Dust Mite (mix) Mold (mix) Dog
sIgE	Cat Dander Fel d 1 Fel d 2 Fel d 4 Fel d 7	**Seasonal allergens:** Timothy Grass **Perennial allergens:** Dog Dander Mite Df Mite Dp Alternaria tenus Cladosporium herbarum Cockroach German

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized descriptively:

- Demographic variables:
  - Age at screening as a continuous variable
  - Age group (Adolescents, Adults)
  - Sex (Male, Female)
  - Race (White, Black, Asian, Other)
  - Ethnicity (Hispanic/Latino: Yes or No)
  - Baseline Weight (kg)
  - Baseline Height (cm)
  - BMI (kg/m^2)
  - Region (Canada, United States, Europe)
- Baseline characteristics:
  - Skin prick test (SPT) for cat (mm)
  - Serum cat dander sIgE and Fel d 1 sIgE at screening and baseline (≥0.7 to <3.5 kUa/L, ≥3.5 to <17.5 kUa/L, ≥17.5 kUa/L)
  - Serum house dust mite Df and Dp sIgE at screening and baseline (< 0.7 kUa/L, ≥0.7 kUa/L)
  - Baseline sensitization status based on sIgE or SPT (e.g., sensitization to cat allergens only, only sensitized to cat allergens and seasonal allergens, only sensitized to cat allergens and perennial allergens, or sensitized to cat allergens, seasonal and perennial allergens)
  - Baseline sensitization status based on sIgE or SPT (mono-sensitized to cat, poly-sensitized)
  - Baseline allergy symptom status for tree, grass, and weeds (as recorded in eCRF)
  - Baseline TNSS, TOSS, TSS, DMS, CSMS
  - Baseline RQLQ(S)
  - Baseline FEV1(L and percent predicted)
  - History of Asthma (yes/no, as recorded in eCRF)
  - Baseline ANSD, ADSD, ADSS, ACQ-5, asthma rescue medication use, and nighttime awakening for asthma patients

- Baseline PGIS
- Duration of allergic symptoms to cat
- Number of cats in home (1, 2, ≥3)

Sensitization status based on sIgE or SPT

An SPT with cat allergen extract, other relevant allergens, a negative control (such as saline/ diluent), and a histamine positive control will be performed to assess sensitization status. A positive response for cat is defined by a mean wheal diameter at least 5 mm greater than a negative control, in which SPT mean wheal diameter is defined as ([longest diameter + longest perpendicular]/2). For other allergens, a positive sensitization by SPT is defined as a mean wheal diameter of at least 3 mm greater than a negative control.

For allergens that are not cat-related, sensitization by sIgE is defined as sIgE ≥0.35.

SPT and sIgE values will be presented as both summaries of continuous measurements and categorically as specified above. Patients will be considered sensitized to an allergen if they meet the criteria defined above for either SPT or sIgE.

4.2. Medical History

Medical history (including general medical history, allergic disease history and history related to aero-allergens) will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).

Information on conditions related to cat allergy will be summarized in medical history, including asthma, allergic conjunctivitis, allergic rhinitis, etc.

4.3. Pre-Treatment / Concomitant Medication/Procedure

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODD). Procedure will be performed based on medical history, adverse event, prophylaxis, and others. Subjects will be counted once in each medication class linked to the medication.

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

Concomitant medications/procedures (CMs/CPs): medications taken or procedures performed following the dose of study drug through the EOS visit.

- Concomitant medications/procedures during the 60-week treatment period are medications/procedures taken after the first dose up to the week 60 visit date or date of study day 421 if the week 60 visit date is missing. Medications/procedures taken during the 60-week treatment period and continued afterwards into the follow-up period will be counted only once as concomitant medications/procedures during the 60-week treatment period.
- Concomitant medications/procedures during the follow-up period are medications/procedures taken after the week 60 visit date or date of study day 421 if the week 60 visit date is missing to end of study.

4.4. Rescue Medication and Prohibited Medication During Study

Medications prohibited throughout the entire study are presented in Table 2 and medications prohibited for specific study periods are presented in Table 3.

Table 2: Medications Prohibited Prior to Screening and Throughout the Study

Medication Group	Time Prohibited Before Study (Washout)
Corticosteroids (intra-muscular/ intra-articular/ extended duration implants such as intravitreal etc.)	Prohibited (3 months)
Tricyclic antidepressants/ typical antipsychotics	Prohibited (14 days)
Specific immunotherapy (SIT) with cat allergen or vaccines against cat allergy	Prohibited (6 months)
SIT with any allergen other than cat	Prohibited
Immune directed biologics and/or therapies that would interfere with Type 2 allergic disease or suppress the immune system, including but not limited to anti-IgE, anti IL-5, anti Il-4	Prohibited (6 months)
Methylxanthines	Prohibited (3 days)
Systemic calcineurin inhibitors	Prohibited (14 days)

Table 3: Medications Prohibited During Specific Periods of the Study

Medication Group	Medication Subgroup	Baseline Assessment Period up to Week 12 and Weeks 48 to 60 (Washout)*
Antihistamines	1st gen, 2nd gen oral antihistamines/ intranasal antihistamines/ ocular antihistamines	Prohibited except study provided anti-allergy rescue medications (desloratadine, olopatadine)
	Longer acting antihistamines (e.g., Hydroxyzine/ Cyproheptadine)	Prohibited (10 days)
Decongestants	Topical/ oral	Prohibited (3 days)
Leukotreine modifiers		Prohibited (30 days)
Anti cholinergics	Intranasal anticholinergics	Prohibited (12 h)
Corticosteroids	Intranasal	Prohibited except study provided anti-allergy rescue medications (mometasone nasal spray)
	Ocular	Prohibited (14 days)
	Oral/ IV	Prohibited (30 days)
Cromoglycates	Ocular/ intranasal	Prohibited (14 days)

* NOTE: Patients will be provided the study rescue medications (desloratidine, olopatadine, mometasone furoate, or in-class equivalent) starting at their baseline assessment visit during screening. Once the patients start their baseline assessment, they should continue to use the study provided rescue medications and avoid any prohibited medications until the completion of the initial efficacy assessment period (weeks 0 to 12). Similarly, the patients should continue to use the study provided rescue medications and avoid any prohibited medications during the final efficacy assessment period (48 to 60 weeks). Prohibited medications (with specific washout durations) are specified in this table for these time periods. Anti-allergic medications (such as antihistamines, anti-allergic eye drops, anti-allergic nasal sprays) outside of study-related anti-allergic medications are prohibited during baseline and efficacy assessment periods (baseline to week 12 and weeks 48 to 60).

Skin prick testing: Antihistamines should be withheld for 5 days prior to SPT (longer acting antihistamines such as hydroxyzine, cyproheptadine should be withheld for 10 days).

Prohibited medications as specified above have been further categorized into groups based on their expected impact on the efficacy variables. Appropriate data handling methods for analysis for each category are described in Section 5.6. Categories of prohibited medications based on their expected impact on efficacy assessment are defined in Section 10.5.

Medications that fall into each of the categories as specified in Section 10.5 are specified in Table 7 (for CSMS, TNSS, TOSS, DMS and RQLQ(S)+12), Table 8 (for asthma-related endpoints), and Table 9 (for SPT endpoints). For medications that fall into Category 2, blinded adjudication by the study medical director will be implemented before the database lock to determine the potential impact of the use of the prohibited medication on the efficacy assessments. The adjudication procedure will be documented.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

The primary efficacy endpoint in the study is the daily CSMS defined in Section 4.5.5, averaged over the last 12 weeks of the treatment period (weeks 48 to 60).

4.5.2. Key Secondary Efficacy Variables

The key secondary endpoints, specified without order, are:

- Daily TNSS, averaged over the last 12 weeks of treatment period (weeks 48 to 60)
- Percent change from pre-treatment baseline in average CSMS, over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from pre-treatment baseline in average TNSS, over the last 12 weeks of the treatment period (weeks 48 to 60)
- Daily TSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from pre-treatment baseline in average TSS, over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from baseline to the end of treatment (week 60) in cat SPT mean wheal diameter

4.5.3. Other Secondary Efficacy Variables

Other secondary endpoints, specified without order, are:

- Daily CSMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Daily TNSS, averaged over the initial 12 weeks of treatment period (weeks 0 to 12)
- Percent change from pre-treatment baseline in average CSMS, over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Percent change from pre-treatment baseline in average TNSS, over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Percent change from pre-treatment baseline in average TSS, over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Daily TSS score, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Percent change from pre-treatment baseline in average TOSS, over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Daily TOSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from pre-treatment baseline in average TOSS, over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from baseline to week 12 in FEV1 in patients with asthma
- Percent change from baseline to week 60 in FEV1 in patients with asthma
- Percent change from baseline to week 12 in cat skin prick test (SPT) mean wheal diameter
- Change from baseline to week 12 in FEV1 in patients with asthma
- Change from baseline to week 60 in FEV1 in patients with asthma
- Change from baseline to week 60 in RQLQ(S)+12
- DMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)
- DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from pre-treatment baseline in average DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)
- Percent change from baseline to end of study (week 72) in cat SPT mean wheal diameter
- Asthma daily symptom score (ADSS), averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), using Asthma Daytime Symptom Diary (ADSD) and the Asthma Nighttime Symptom Diary (ANSD), in patients with asthma

- Asthma daily symptom score (ADSS), averaged over the last 12 weeks of the treatment period (weeks 48 to 60), using Asthma Daytime Symptom Diary (ADSD) and the Asthma Nighttime Symptom Diary (ANSD), in patients with asthma
- Daily TOSS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Change from baseline to week 60 in ACQ-5 in patients with asthma
- Daily number of nighttime awakenings, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma
- Daily number of nighttime awakenings, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients with asthma

4.5.4. Exploratory Variables

The exploratory endpoints are:

- The number of "well days" over the initial 12 weeks (weeks 0 to 12) of the treatment period; "well days" are defined as days when rescue medication is not utilized and the TSS is ≤2/18
- The number of "well days" over the last 12 weeks of the treatment period (weeks 48 to 60); "well days" are defined as days when rescue medication is not utilized and the TSS is ≤2/18
- Percent change from pre-treatment baseline in average ADSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), using ADSD and the ANSD
- Percent change from pre-treatment baseline in average frequency of asthma rescue medication use, defined as the number of puffs of a short-acting bronchodilator and an inhaled steroid over the past 24 hours, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma
- Percent change from pre-treatment baseline in average frequency of nighttime awakenings, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma
- Percent change from pre-treatment baseline in average DMS, over the initial 12 weeks of the treatment period (weeks 0 to 12)
- Change from baseline to week 12 in RQLQ(S)+12
- Change from baseline to week 12 in Asthma Control Questionnaire 5 Question Version (ACQ-5) in patients with asthma
- Daily frequency of asthma rescue medication use, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma
- Daily frequency of asthma rescue medication use, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients with asthma

4.5.5. Definitions

The definition and details of the efficacy variables are listed as follows:

Total Nasal Symptom Score (TNSS)

The TNSS ranges from 0 to 12 and is based on assessment of 4 nasal symptoms graded on a Likert scale ranging from 0 (none) to 3 (severe) for nasal congestion, itching, and runny nose, and sneezing. The TNSS will be recorded before going to bed for the night using an e-diary.

Total Ocular Symptom Score (TOSS)

The TOSS ranges from 0 to 6 and is based on 2 eye symptoms: itching/redness/gritty feeling and tearing/watering. Each of the 2 symptoms is graded on a Likert scale ranging from 0 (none) to 3 (severe). The TOSS will be recorded before going to bed for the night using an e-diary.

Total Symptom Score (TSS)

The daily TSS is calculated by adding the TNSS and TOSS together, for a combined TSS of 0 to 18.

Daily Medication Score (DMS)

For the DMS, before going to bed for the night, patients will be asked to record their daily rescue medication use using an e-diary, including which medications and the amount of these pre-specified medications. This information will be used to calculate the DMS for the following medications or the approved in-class equivalents, as follows: desloratadine 5 mg 6 points/dose; maximum daily score 6 points, olopatadine 1 mg/mL each drop 1.5 points/drop; maximum daily score 6 points, mometasone furoate 50 ug/dose 2.0 points/spray; maximum daily score 8 points). The maximum DMS score is 20 (Calderon, 2014).

Combined Symptom and Medication Score (CSMS)

The daily CSMS is calculated by adding the DMS and TSS together, with scores ranging between 0 and 38. The method for calculating average CSMS is described in Section 5.6.1.

Skin Prick Test

An SPT with cat allergen extract, other relevant allergens, a negative control (such as saline/ diluent), and a histamine positive control will be performed to assess sensitization status. A positive response for cat is defined by a mean wheal diameter (MWD) at least 5 mm greater than a negative control, in which SPT MWD is defined as ([longest diameter + longest perpendicular]/2). (Note: For other allergens, a positive sensitization is defined as a MWD of at least 3 mm greater than a negative control.)

The negative control mean wheal diameter will be subtracted from the SPT mean wheal diameter for presentation as a normalized MWD. In the case that the negative control MWD is larger than the allergen SPT MWD, the value of 0 mm will be used as the normalized MWD.

After week 12, the cat, house dust mite, and negative control SPT will be performed in replicate. Averages of the MWDs will be calculated for each allergen at the same visit and then the average of the two negative control MWDs will be subtracted to compute the normalized MWD.

Standardized Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ(S)] for Ages 12+

The RQLQ(S) is a self-administered questionnaire to measure HRQoL in those 12 years of age and above, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: activity limitation, sleep problems, nasal symptoms, eye symptoms, non-nasal/eye symptoms, practical problems, and emotional function. The RQLQ(S) responses are based on a 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). The overall RQLQ(S) score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains. Higher scores indicated more HRQoL impairment (lower scores were better). A change of 0.5 point or more in total score is considered to be clinically meaningful.

Asthma Nighttime Symptom Diary Score

Only for patients with asthma, upon waking up in the morning, patients will complete the e-dairy to report asthma symptoms experienced during the nighttime using the Asthma Nighttime Symptom Diary (ANSD). The ANSD score will be based on 6 patient-reported symptoms (difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough at their worst using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine').

Asthma Daytime Symptom Diary Score

Only for patients with asthma, before going to bed for the night, patients will complete the e-diary to report asthma symptoms experienced during the day using the Asthma Daytime Symptom Diary (ADSD). The ADSD score will be based on 6 patient-reported symptoms (difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough at their worst using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine').

Asthma Daily Symptom Score

Only for patients with asthma, average of daily scores of the ANSD score and the ADSD score will be used to generate an Asthma Daily Symptom Score (ADSS) ranging from 0 ('None') to 10 ('As bad as you can imagine').

Juniper Asthma Control Questionnaire

Only for patients with asthma, the ACQ-5, (5-question version of the Juniper ACQ), is a validated questionnaire to evaluate asthma control. The ACQ-5 score is the mean of the scores of the 5 items and ranges from 0 (totally controlled) to 6 (severely uncontrolled). Scores less than 1.0 reflect adequately controlled asthma, and scores 1.0 or greater reflect inadequately controlled asthma. Higher score indicates lower asthma control and 0.5 is the smallest change that can be considered clinically important.

FEV1

Before randomization, in-clinic spirometry will be performed on all patients to determine FEV1 (forced expiratory volume in 1 second) in liters (L). After randomization, in-clinic spirometry will only be performed for patients with asthma.

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)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA).

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. Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

For safety variables, 4 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the last dose of study drug plus 12 weeks (visit 3 to visit 14).
- The follow-up period is defined as the end of the on-treatment period to 12 weeks after the end of the on-treatment period (visit 14 to visit 15).
- The overall study period is defined as the day from first dose of study drug to the end of study visit (on-treatment period plus follow-up period)

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment and follow-up periods.

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in the study protocol 10.2.2.

4.6.2. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. List of AESI and AESI criteria is specified in Section 10.4.

Adverse events of special interest for this study include:

- Severe or systemic hypersensitivity reactions (including anaphylaxis) defined using the narrow SMQ for hypersensitivity, with blinded manual adjudication of relevant PTs by medical monitor before database lock.
  - For SMQ "anaphylactic reaction", an algorithmic approach will be used. Details are provided in Section 10.4.
- Asthma exacerbations defined using the narrow SMQ for asthma and further manual blinded adjudication before database lock for events requiring treatment with systemic corticosteroids or resulting in an emergency room visit or hospitalization.

4.6.3. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected. Tests will include:

Blood chemistry

Sodium	Total protein, serum	Aspartate aminotransferase (AST)
Potassium	Creatinine	Alanine aminotransferase (ALT)
Chloride	Blood urea nitrogen (BUN)	Alkaline phosphatase
Carbon dioxide	Total bilirubin	Albumin
Calcium	Glucose	

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	WBC
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Yeast
Protein		

Other laboratory tests

4.6.4. Vital Signs

Vital signs include systolic and diastolic blood pressure, respiratory rate, and heart rate. Vital signs will be collected in a seated position. On the day of study drug administration, vital signs are taken prior to PK blood draw, prior to study drug administration, and at 2 hours (±10 min) after completion of the injection.

Weight and height are measured at screening visit 1 only.

4.6.5. Physical Examination Variables

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

4.6.6. Spirometry

Spirometry measurements include FVC (L), FEV1 (L), FEV1/FVC, PEF (L/s), FEF 25-75 (L/s). Spirometry (American Thoracic Society [ATS]/European Respiratory Society [ERS]-compliant) (Graham, 2019), as adjudicated during the centralized OverRead review, will be performed locally during the study at specified time points. Spirometry details will be available in a separate operational manual provided to the sites. Additional data handling conventions are presented in Section 6.3.

4.7. Pharmacokinetic Variables

Concentrations in serum of total (free+antigen bound) REGN1908 and REGN1909 will be determined at time points specified in the study schedule of events in Appendix Section 10.2. Pharmacokinetic variables consist concentrations individual drug (REGN1908 and REGN1909), and total drug (REGN1908+REGN1909) in serum, and time (both nominal and actual time).

4.8. Immunogenicity Variables

The immunogenicity variables include ADA status, titer and NAb status at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2. Samples positive in the REGN1908-1909 ADA assay will be further characterized for ADA titers. Anti-REGN1908, and anti-REGN1909 neutralizing antibodies (NAb) analysis may be performed on ADA-positive serum samples. The overall immunogenicity risk will be taken into consideration to assess the need for NAb analysis. Serum samples will be banked, if NAb analysis is to be conducted at a later time.

4.9. Biomarker Variables

Exploratory biomarker variables include:

- Serum for specific IgE for Fel d 1
- Serum for specific IgE for cat dander
- Serum for sIgE for Fel d 2, 4, and 7 at baseline, week 12 (V6), week 60 (V14)
- Serum for sIgE for other allergens (e.g., HDM, etc.)

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, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. Missing values at baseline will not be imputed unless otherwise specified.

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups and overall based on the FAS.

5.2. Medical History

Medical history will be summarized by primary SOC and PT for each treatment group and for study total based on the SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups. Number/proportion of each medical history, listing all the values in allergy form.

5.3. Prior/Concomitant Medications/Procedures

The number and proportion of subjects taking prior medications will be summarized, as well as the number and proportion taking concomitant medications during the treatment and follow-up periods (separately) based on the FAS. Similar tables will be provided for the number and proportion of subjects taking prohibited medications. Prohibited medications taken in the first and last 12 weeks of the treatment period may also be presented separately. Each table will be sorted by decreasing frequency of Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4 based on the overall incidence. Subjects will be counted only once for each medication class (ATC levels 2 and 4) linked to the medication.

Number of patients taking rescue medications will be summarized by medication name based on rescue medication e-diary based on the FAS. The frequency of rescue medication use during the efficacy assessment periods may also be summarized.

Number and proportion of patients taking prior/concomitant procedures will be summarized for study total based on the SAF, sorted by decreasing frequency of SOC and PT based on the overall incidence. Patients will be counted only once for each SOC and PT linked to the procedure. Number of patients receiving prior immunotherapy (SLIT, SCIT) will be summarized separately.

5.4. Subject Disposition

The following summaries will be provided for each treatment group and total (unless otherwise specified):

- The total number of screened subjects who signed ICF, along with reasons for screen failure (for study total only)
- The total number of randomized patients: received a randomization number from IWRS
- The total number of patients in each analysis set
- The total number of randomized patients who discontinued the study and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of randomized patients who completed the study treatment and discontinued the study treatment with the reason of discontinuation (including COVID-19 related reasons)

5.5. Extent of Study Treatment Exposure

5.5.1. Exposure to Investigational Product

The duration of exposure during the study will be calculated as follows:

(date of last dose of study drug– date of first dose of study drug) + 84 days

The calculations do not take into account temporary dosing interruption including due to COVID-19. The summary of exposure to study drug will include the number of study drug doses and injections administered and the duration of exposure. Duration of exposure will be summarized for each treatment group using the number of patients, mean, SD, minimum, median, Q1, Q3, and maximum.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories cumulatively by these categories: ≥ 85 days (> 12 weeks), ≥ 169 days (> 24 weeks), ≥ 253 days (> 36 weeks), ≥ 337 days (> 48 weeks), and ≥ 365 days (> 52 weeks).

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 duration of observation period will be summarized descriptively using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest are specified as:

< 85 days, ≥ 85 days, ≥ 169 days, ≥ 253 days, ≥ 337 days, ≥ 421 days, and ≥ 505 days.

5.6. Analyses of Efficacy Variables

5.6.1. Analysis of Primary Efficacy Variable

The analyses of efficacy variables are described in the subsections below and summarized in Section 10.1.1 of the Appendix. The intercurrent events, strategies, and the corresponding missing data handling approaches for the primary estimands of interest for the primary endpoint are provided in Table 4.

Table 4: Summary of Estimand for Primary Endpoint

Endpoint Category	Estimand			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary endpoint	Daily combined symptom and medication scores (CSMS) averaged over the last 12 weeks of the treatment period	FAS	The intercurrent events will be handled as follows[1]: 1. Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) 2. Rescue treatment and select prohibited medications[2,3] taken to treat allergic symptoms during the last 12 weeks of the efficacy assessment period: data after medication will be used in the analysis (treatment policy strategy) 3. Prohibited medications taken during the efficacy assessment period which are adjudicated to be handled using a composite strategy[3]: a. The daily CSMS, starting from the day the prohibited medication was taken through the end of the last 12 weeks of efficacy assessment, will be imputed by worst CSMS score (largest observed TNSS+TOSS+DMS) observed before prohibited medications were taken from the same patient. The average CSMS will be calculated using observed components prior to receiving prohibited medication and imputed values after prohibited medication. b. If no values of CSMS[4] are available during the last 12 weeks of the efficacy assessment period prior to the patient taking prohibited medication, the daily CSMS will be imputed using the worst average CSMS score during the last 12 weeks of all observations in the corresponding treatment group 4. Prohibited medications taken during the efficacy assessment period which are adjudicated to be handled using a hypothetical strategy[3]: data during use of medication and during washout period will be set to missing 5. Change in cat allergen exposure: a. If no cat is living in the patient's home during all or part of the last 12 weeks of the treatment period: all available data will be used in analysis (treatment policy) b. If patient travels away from home for less than 42 consecutive days: all available data will be used in	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and baseline CSMS as a covariate. The least squares means (LS-means) estimates for the average CSMS during the last 12 weeks of the treatment period for each treatment group, as well as the difference between the REGN1908-1909 and placebo will be provided along with the corresponding 2-sided p-value and associated 95% confidence interval.

Endpoint Category	Estimand			
	Endpoint(s)	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
			analysis (treatment policy); otherwise, for travel ≥ 42 consecutive days, a hypothetical strategy will be used where data during patient travel will be set to missing In addition, the missing data imputation rules for patients who have no available values of CSMS[4] during the last 12 weeks of the treatment period are as follows: • Missing data due to patients'discontinuation from study due to AEs and lack of efficacy will be imputed using worst average CSMS score during the last 12 weeks of all observations in the corresponding treatment group • Missing data due to any other reason will be imputed using MI	
[1] If a data point or missing value falls into multiple categories of intercurrent events as specified above, the following priority order for handling of data will be applied: ICE 3), ICE 4), ICE 5b) ICE 5a), ICE 1), ICE 2). For example, if data or missing value fall into both ICE 3) and 5a), the strategy for ICE 3) should be followed, as it takes priority over 5a). [2] Select prohibited medications that will be handled using a treatment policy are listed in Category 1 of Table 7 [3] Additional prohibited medications listed in Category 2 Table 7 will undergo blinded adjudicated by study medical monitor before the database lock to determine if they will be handled by treatment policy, composite strategy, or hypothetical strategy [4] No available values of CSMS means no available TNSS, TOSS, or DMS during the last 12 weeks of the efficacy assessment period				

The primary analysis will focus on the comparison between REGN1908-1909 and placebo in the FAS. The analysis will be performed using an analysis of covariance (ANCOVA) model, with the treatment group, randomization stratification factors (as stratified), and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed effects and the baseline CSMS as a covariate. The baseline CSMS will be calculated as the average CSMS during the first 15 consecutive days of the baseline assessment period where eligibility criteria (for TSS and rescue medication use) were met, as specified based on the following two criteria:

1. Must have at least 8 unique days of a TSS score ≥ 8 within a 15 consecutive day period.
2. Must have a least 8 unique days of a DMS score >0 within the same 15 consecutive day period as Criteria 1. The 8 unique days do not have to occur on the same days as Criteria 1; however, they must be within the same 15 consecutive days.

If less than 15 days of data are available during the baseline assessment period, the baseline will be the average CSMS over all available days (if duplicate entries of CSMS are available on the same day, the worst score will be used).

Only days with observed data will be included in the calculation of average score. The average CSMS (max score 38/day) will be calculated based on the sum of average daily TNSS (max score 12/day), average daily TOSS (max score 6/day) and average daily medication scores (DMS, max of 20/day) recorded over the last 12 weeks of the treatment period (weeks 48 to 60).

For the MI procedure, missing data (the average CSMS) will be imputed 50 times to generate 50 complete data sets utilizing the SAS procedure PROC MI. Note that any imputation by worst CSMS score as specified in Table 4 will occur prior to MI. The 2 steps below will be followed for MI:

Step 1: The Markov Chain Monte Carlo (MCMC) method will be used to fill in missing values of average CSMS during weeks 0-12 by treatment group so that a monotone missing pattern will be formed.

Step 2: Using the data sets from Step 1, missing values of average CSMS from weeks 48-60 will be imputed using a monotone regression method. The imputation model will include the covariates in the ANCOVA model and the average CSMS from weeks 0-12.

For steps 1 and 2, any score imputed outside the range of CSMS (0-38) will be truncated to the nearest value of CSMS according to the following algorithm:

- If the imputed score > 38, then the final imputed score will be 38.
- If the imputed score < 0, then the final imputed score will be 0.

Sample SAS syntax code for MI:

```
proc mi data=mi1 out=mi3 noprint nimpute=50 seed=190819;
mcmc impute=monotone;
var BASELINE CSMS012 CSMS4860;
by TRTP;
run;
proc mi data=mi3 out=mi4 nimpute=1 seed=190819;
class TRTP STRAT1 STRAT2 STRAT3 CATIGE;
monotone reg;
var TRTP STRAT1 STRAT2 STRAT3 CATIGE BASELINE CSMS012;
by _imputation_;
run;
```

Each imputed data set will then be analyzed by ANCOVA as previously described. The SAS procedure PROC MIANALYZE will be used to generate valid statistical inferences by combining results from these 50 ANCOVA analyses using Rubin's formula. The least squares means (LS-means) estimates for the average CSMS during the last 12 weeks of the treatment period for each treatment group, as well as the difference between the REGN1908-1909 and placebo will be provided along with the corresponding 2-sided p-value and associated 95% confidence interval.

Sensitivity analysis:

With respect to the missing data handling of daily entries, sensitivity analyses will be performed to confirm robustness of the conclusion drawn based on the main model for primary analysis.

Tipping Point Analysis

Sensitivity analysis using a tipping point approach with MI will be performed to assess the robustness of the results due to data that may be missing not-at-random (MNAR). The impact from missing data on comparisons of average CSMS during the last 12 weeks between REGN1908-1909 and placebo will be examined.

This approach will introduce a sensitivity parameter, δ. Estimations will be performed using MI methodology. Missing data will be imputed 50 times to generate 50 complete data sets utilizing the SAS procedure PROC MI for each δ following the 2 steps as previously described, where δ will be added to each of the imputed values (of average of last 12 weeks) for patients in the REGN1908-1909 arm. (Note that when δ=0, this aligns with the standard MI analysis assuming missing at random (MAR).) Scores that are adjusted to outside the range of CSMS will be truncated in the same manner as previously described for the MI method.

Each imputed data set will then be analyzed by ANCOVA as previously described. For each δ, the SAS procedure PROC MIANALYZE will be used to generate valid statistical inferences by combining results from these 50 ANCOVA analyses using Rubin's formula. By progressively increasing δ, the sensitivity analysis will explore the "tipping point", where the result is no longer statistically significant (i.e., p-value>0.049).

Additional Sensitivity Analyses

An additional sensitivity analysis may be performed when determining asthma status from medical history and house dust mite sensitization status from lab data, rather than as stratified.

Supplemental Analyses

Additional sensitivity analysis will also be performed for the handling of data after relevant prohibited medications. After use of prohibited medication, daily CSMS will be imputed by the worst score in the corresponding treatment group, and with the worst 5^{th} percentile score in the corresponding treatment group, as a way to consider a reasonable range of "poor" scores to impute the missing data.

A supplemental analysis will also be performed where all intercurrent events are handled via a treatment policy, regardless of type of prohibited medication taken or change in cat exposure.

5.6.2. Analysis of Secondary Efficacy Variables

The secondary efficacy endpoints will be analyzed using an ANCOVA model in the same fashion as the primary analysis of the primary endpoint.

Average Daily Symptom Score Endpoints (TOSS, TNSS, DMS, TSS)

The average TOSS, TNSS, and DMS will be calculated using all observed daily scores during the specified time period (initial 12 weeks or last 12 weeks of the treatment period).

The average TSS will be calculated by adding average TNSS and average TOSS during the specified time period (initial 12 weeks or the last 12 weeks of the study).

The intercurrent events, strategies, and the corresponding missing data handling approaches for these endpoints will follow the same strategy as for the primary endpoint, outlined in Table 4.

Supplemental analyses using non-parametric methods, such as Wilcoxon ranked sum test or Hodges-Lehmann analysis of median differences, may be performed in the event of a violation of the normality assumption.

Asthma-related endpoints (ADSS, FEV1, ACQ-5)

All asthma endpoints will be analyzed on patients in the FAS with asthma (all randomized patients with ongoing asthma in medical history). Supplemental analyses may be performed in the subset of ongoing asthma patients who were also on asthma medication at baseline.

All available daily ADSS will be averaged over the specified time period (initial 12 weeks or last 12 weeks of the treatment period). If ADSD or ANSD is missing on any given day, ADSS score for that day will be considered missing and no value will be calculated. In addition, ANSD will be shifted by one day, i.e., ADSD on Day 1 and ANSD on Day 2 will be used to get the ADSS on Day 1, ADSD on Day 2 and ANSD on Day 3 will be used to get the ADSS on Day 2, and so on. The day before Visit 6 or Visit 14 for the initial 12 weeks and last 12 weeks, respectively, will be the last day that contributes to the average ADSS (since there will generally be no ANSD measurement corresponding to the date of Visit 6 or 14).

The estimand for ADSS will follow the same approach as for the primary endpoint, described in Table 4. Separate analyses of average ADSD and average ANSD may also be performed.

Estimands for FEV1 and ACQ-5 are specified in Table 5. A supplemental analysis may be performed for the change from baseline ACQ-5 endpoint only in patients with baseline ACQ-5 > 1.5.

Supplemental analyses using non-parametric methods, such as Wilcoxon ranked sum test or Hodges-Lehmann analysis of median differences, may be performed in the event of a violation of the normality assumption.

Prohibited medications and corresponding data utilization methods relevant for asthma endpoints are specified in Table 8

SPT endpoints

The intercurrent events, strategies, and the corresponding missing data handling approaches for the SPT endpoints are outlined in Table 5.

Prohibited medications and corresponding data utilization methods relevant for SPT endpoints are specified in Table 9

Table 5: Summary of Estimands for Secondary Endpoints of Clinical Importance

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Secondary endpoint – Continuous, SPT, and RQLQ(S)+12	Percent change from baseline to week 12 and end of treatment (week 60) cat SPT mean wheal diameter Change from baseline to week 60 in RQLQ(S)+12	FAS	The intercurrent events will be handled as follows[5]: 1. Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) 2. Rescue treatment[1] and select prohibited medications[2,4] to treat allergic symptoms during the efficacy assessment period: data after allergy-relieving rescue medication will be used in the analysis (treatment policy strategy) 3. Prohibited medications taken during the protocol defined window leading up to the relevant visit (week 12 or week 60) which are adjudicated to be handled using a composite strategy[4]: data will be set to missing and imputed using the worst value of all observations in corresponding treatment group. 4. Prohibited taken during the protocol defined window leading up to the relevant visit (week 12 or week 60) which are adjudicated to be handled using a hypothetical strategy[3,4]: data will be set to missing and multiple imputation will be used. 5. Patient does not have exposure to cat leading up to assessment[6]: a. If no cat is living in the patient's home leading up to assessment: all available data will be used in analysis (treatment policy) b. If patient is traveling away from home for less than 42 consecutive days prior to the assessment: all available data will be used in the analysis (treatment policy); otherwise (for travel ≥42 consecutive days), data will set to missing and multiple imputation will be used (hypothetical strategy)	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and relevant baseline measurement as a covariate. LS-means estimates will be provided for each treatment group, as well as the difference between REGN1908-1909 and placebo with corresponding 95% confidence interval and 2-sided p-value.
Secondary endpoint – Continuous, FEV1, and ACQ-5	Percent change from baseline to week 12, week 60 FEV1 Change from baseline to week 60 in ACQ-5	FAS with asthma		

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
			In addition, if a patient has no available value of the relevant measurement at the specified visit, the imputation rules are as follows: • Missing data because of patients' discontinuation from study due to AEs and lack of efficacy will be imputed using worst score of all the observations in corresponding treatment group • Missing data due to any other reason will be imputed using MI.	

[1] Note that for SPT endpoints, oral antihistamines are considered as prohibited medication, as specified in Table 9

[2] Category 1 of Table 7 (RQLQ), Table 8 (asthma), Table 9 (SPT) lists prohibited medications that will be handled using a treatment policy

[3] Additional prohibited medications listed in Category 2 of Table 7, Table 8, and Table 9 will undergo blinded adjudication by study medical monitor before the database lock to determine they will be handled by treatment policy, composite strategy, or hypothetical strategy

[4] Prohibited medications that are not indicative of treatment failure and will be handled by hypothetical strategy are defined in Category 3 of Table 8 and Table 9

[5] If a data point or missing value falls into multiple categories of intercurrent events as specified above, the following priority order for handling of data will be applied: ICE 3), ICE 4), ICE 5b), ICE 5a), ICE 1), ICE 2). For example, if data or missing value fall into both ICE 3) and 4), the strategy for ICE 3) should be followed, as it takes priority over ICE 4).

[6] This intercurrent event is not relevant for the SPT endpoints

5.6.3. Adjustment for Multiple Comparisons

A non-binding futility interim analysis (IA) is planned in this study (details are provided in Section 7) and an administrative penalty of 0.001 will be taken from the significance level used at final analysis, and thus 2-sided 0.049 will be used. No further multiplicity adjustment will be performed for the IA.

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.049 for the primary endpoint and the secondary endpoints of R1908-1909 versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.049 significance level. The hierarchical testing order is shown in below table (all comparisons are with the placebo).

Level	Endpoints	Testing Order
Primary endpoint	Daily CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)	1
Secondary endpoints	Daily TNSS, averaged over the last 12 weeks of treatment period (weeks 48 to 60)	2
	Percent change from baseline to the end of treatment (week 60) in cat SPT mean wheal diameter	3
	Percent change from pre-treatment baseline in average TNSS, over the last 12 weeks of the treatment period (weeks 48 to 60)	4
	Daily CSMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)	5
	Daily TNSS, averaged over the initial 12 weeks of treatment period (weeks 0 to 12)	6
	Daily TSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)	7
	Daily TSS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12)	8
	Percent change from pre-treatment baseline in average CSMS, over the last 12 weeks of the treatment period (weeks 48 to 60)	9
	Change from baseline to week 60 in RQLQ(S)+12	10
	DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)	11
	Daily TOSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)	12
	Percent change from pre-treatment baseline in average TSS, over the last 12 weeks of the treatment period (weeks 48 to 60)	13

5.6.4. Subgroup analysis

Subgroups defined in Section 3.5 for the primary endpoint will be analyzed based on the FAS.

The analysis method for the subgroups will be the same as the primary analysis described in Section 5.6.1, as appropriate. If for any reason, such as small number of patients in a subgroup, the model-based inferential statistics cannot be computed, or deemed inappropriate, only descriptive statistics will be provided.

Forest plots of the primary efficacy endpoint across subgroups will be provided.

5.6.5. Analysis of Exploratory Efficacy Variables

For continuous exploratory efficacy variables, e.g., percent change in ADSS, they will be analyzed by using an ANCOVA model similar to the analyses of primary endpoint.

5.7. Analysis of Safety Data

The analysis of safety will be performed on the SAF, as defined in Section 3.2.

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

Thresholds for treatment-emergent Potential Clinically Significant Values (PCSV) in laboratory variables and vital signs are defined in Section 10.3. Treatment-emergent PCSV is any PCSV that developed or worsened in severity compared to the baseline during the on-treatment and follow-up period. The baseline when determining treatment-emergent PCSV refers to the baseline value of the study.

The summary of safety results will be presented for each treatment group. The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

In addition, the summary of safety results (including TEAEs, clinical laboratory, vital signs, and ECG) will be performed for subjects who were impacted by COVID-19 pandemic and not impacted by COVID-19 pandemic in each study part, respectively if deemed appropriate. The summary will be performed for pre-, during, and post-COVID-19 periods for patients impacted by COVID-19, if deemed appropriate.

5.7.1. Adverse Events

The number and proportion of subjects reporting TEAEs will be summarized on SAF overall during the study, during the week 60 treatment period, during the follow-up period, and during the study, separately. The TEAE search criteria is described in Section 3.2.

AE incidence tables will be presented by treatment group for the SAF as well as subgroups for safety. TEAE summaries will present the number (n) and percentage (%) of subjects experiencing a TEAE by SOC, HLT, and PT, sorted by decreasing frequency of SOC, HLT, and PT for the REGN 1908-1909 treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of subjects in each treatment group for safety analysis.

An overall summary of TEAEs will be provided with number and proportion of subjects with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)
- Serious TEAE leading to death
- Study drug related TEAE
- TEAE leading to study treatment discontinuation

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by PT
  - TEAEs by severity and by primary SOC/PT
  - TEAEs related to study drug as assessed by the investigator by primary SOC/PT
  - Severe TEAEs by SOC/PT
  - Severe TEAEs related to study drug as assessed by the investigator by SOC/PT
  - Injection site reactions by HLT/PT
- Serious TEAE
  - Serious TEAEs by primary SOC/PT
  - Serious TEAEs related to study drug as assessed by the investigator by SOC/PT
- Fatal TEAEs by primary SOC/PT
- TEAE leading to study treatment discontinuation by primary SOC/PT
- AESI by AESI category (see Section 10.4), primary SOC/HLT/PT

In order to detect any AE signals, the hazard ratio (HR) may be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events during the 60-week treatment period. Hazard ratios will be calculated using a Cox model including factors of treatment group and randomization strata. For patients with events, the time to events is defined as the date of first event – the date of first dose + 1. Patients without an event will be censored at the end of study period. Graphs of cumulative incidence rate over time may be provided by treatment group for selected TEAEs leading to permanent discontinuation of study treatment.

5.7.2. 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 will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment emergent PCSVs. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF, patients who did not meet the PCSV criterion 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

The graph of mean change and/or percent change from baseline value for lab parameters by visit will be provided.

5.7.3. Analysis of Vital Signs

Summary of vital sign variables (pulse rate, blood pressures, respiratory rate, and temperature) will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

The last measurement will be used in the analysis if multiple data collected at the same time point.

5.8. Analysis of Pharmacokinetic Data

Descriptive statistics of total REGN1908, total REGN1909, and total drug (REGN1908+REGN1909) concentrations in serum at each sampling timepoint will be provided. Plots of mean concentration versus nominal time may be presented. Select PK parameters may be calculated.

Exposure-response analysis for biomarkers, efficacy, and safety endpoints may be conducted as appropriate, and presented in separate reports.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category and maximum titer observed in patients in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as < 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.
- The ADA category of each positive patient is classified as:
- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value

- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
- The maximum titer category of each patient is classified as:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)
- The following will be summarized by treatment group and ADA titer level:
  - Number (n) and percent (%) of ADA-negative patients
  - Number (n) and percent (%) of pre-existing patients
  - Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
  - Number (n) and percent (%) of treatment-boosted ADA positive patients
- Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent, and treatment-boosted ADA response.

5.9.2. Analysis of NAb Data

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis set will be provided by treatment groups. The NAb status is categorized as follows:

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to REGN1908 and REGN1909 will be explored by treatment groups. Plots of individual REGN1908 and REGN1909 concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category and NAb status on these profiles.

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow]) followed by manual adjudication (same as AESI 'Hypersensitivity'))

a) Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow] and identified by an algorithmic approach) followed by manual adjudication if needed. Details for the algorithmic approach are provided in Section 10.4.

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive patients/subjects
- NAb positive

5.11. Analysis of Biomarker Data

All biomarker analyses will be performed on the FAS using all observed data.

Descriptive statistics for the observed values and change and percent change from baseline in detectable allergen specific IgE by treatment and visit will be provided for the biomarker variables.

Baseline serum total IgE, serum cat dander sIgE, serum Fel d 1 sIgE, serum Fel d 2 sIgE, serum Fel d 4 sIgE, serum Fel d 7 sIgE, and the ratio of serum Fel d 1 sIgE/ serum cat dander sIgE will be correlated to the primary and secondary clinical efficacy endpoints using spearman's rho test.

The percent of detectable IgE at each visit (V5 and V7) compared to baseline may also be correlated to the primary and secondary clinical efficacy endpoints using spearman's rho test. Both the spearman correlation coefficients and p-values will be reported. Multiple linear regression models may also be used to explore these relationships, with the efficacy endpoints as dependent variables and the IgE values at baseline (log transformed if appropriate) as dependent variables.

The poly-allergen sensitization status for each study subject will be determined by the number of allergen-specific IgE values that are equal to or above 0.35kUa/L. The number of allergens that each subject was sensitized to will be correlated with the primary and secondary clinical outcomes.

5.12. Sample Size Adjustment

Once at least 50% of patients are enrolled, if the observed blinded standard deviation (SD) for CSMS during the initial 12 weeks is greater than a 5% increase over the assumed SD (6.2), sample size may be increased accordingly, see Appendix Section 10.6. If the SD is lower than the current assumption (6.2), then no adjustment will be made. Similar methods may be considered if the SD of TNSS is larger than a 5% increase over the assumed SD (2.3).

6. DATA CONVENTIONS

The following analysis conventions 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 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. Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data are below the lower limit of quantification (LLOQ)/limit of linearity, half 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.

For efficacy endpoints defined as percent change from baseline, if both baseline and post-baseline values are 0s, the percent change from baseline will be 0; if baseline value is 0 and post-baseline value is a positive number, the percent change from baseline will be assigned by 100%. Missing baseline values for efficacy endpoints will be imputed using the average baseline value across all patients.

6.3. Data Handling Convention for Spirometry Data

This applies to the selection of the FEV1 and FVC values to be used in analysis. As part of a central OverRead review, the best FEV1value and best FVC value will be identified from multiple spirometry efforts performed at the same time. Additionally, spirometry measures will be classified during the OverRead as Acceptable, Borderline Acceptable or Unacceptable.

In the event that the best value at the baseline visit is graded as Unacceptable, the best spirometry effort from a prior screening visit that is graded as Acceptable or Borderline Acceptable should be considered the baseline value. If all available values prior to first administration of study drug are graded as Unacceptable, the baseline value should be set to missing.

Similarly, for post-baseline visits, if all available values are graded as Unacceptable, the data from that visit should be set to missing. Otherwise, the best value should be used in the case of multiple efforts performed at the same time.

6.4. 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.

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.6.1 and Section 5.6.2.

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 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 be used to 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 AE start month is the same as first dose month, then AE start day will be imputed using the day of first dose. If this leads to a date after the AE end date, AE end date will be used instead. If AE start year is the same as first dose year and AE start month different from first dose month, AE start day will be imputed using the first day of the month. If this leads to a date before informed consent date, 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 before the first dose year, the informed consent day and month will be used. If AE start year is the same as first dose year, the first dose day and month will be used. If this leads to a date after AE end date, AE end date will be used instead. If AE start year is after the first dose year, January 1st will be used. Imputation flag is 'M'.

If AE start year is missing: The date of first dose will be used. If this leads to a date after the AE end date, AE end date will be used 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 start date imputation, 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: AE end date will be imputed using the last day of the month. If this leads to a date after end of study follow up date, the end of follow up date will be used instead.

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

If AE end year is missing: AE end date will be imputed using end of follow up date.

Medication start and end date missing

To determine whether a medication is prior 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 listing.

Prior medication start date

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

If start month is missing, and start year is not missing: the day and month will be imputed using January 1st. Imputation flag is 'M'.

If start year is missing: the start date will be imputed using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, to simplify the programming flow, the imputation is proposed to align with 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: the end date will be imputed using the last day of the month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used. Imputation flag is 'D'.

If end month is missing, and end year is not missing: the end date will be imputed using December 31st as the day and month. If this leads to a date on or after first dose intake date, the first dose intake date – 1 will be used instead. Imputation flag is 'M'.

If end year is missing: the end date will be imputed 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: the end date will be imputed using the last day of the month. If this leads to a date after end of study follow up date, the end of follow up date will be used. Imputation flag is 'D'.

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

If end year is missing: the end date will be imputed 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 data manager and study medical director.

PCSV

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

6.5. Visit Windows

Data collected by daily diary will be summarized by the study treatment period (the initial 12 weeks, or the last 12 weeks). The last (initial) 12 weeks will be defined as below:

Treatment period	Collected days >= 84*	Collected days < 84
Initial 12 weeks	[date of Visit 3, date of Visit 3 + 84)	[date of Visit 3, date of Visit 6)
Last 12 weeks	[date of Visit 12, date of Visit 12 + 84)	[date of Visit 12, date of Visit 14]

* Collected days = (date of visit 6– date of visit 3 + 1) for the initial 12 weeks ; Collected days = (date of visit 14– date of visit 12 + 1) for the last 12 weeks.

Data analyzed by-visit-analysis (efficacy [excluding daily diary data], laboratory data, vital sign) 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 analysis visit windows are created per study Schedule of Events (SOE) table for each parameter and will be applied if the data from study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or ET visit mapping for each parameter.

1. If ET due to an AE or lack of efficacy, the ET data for efficacy will not be mapped and the next scheduled visit data will be imputed using the worst score of all the observations in corresponding treatment group; if ET due to random reason, the ET data for efficacy will be mapped using rule 2 below. (Safety data will be mapped in either scenario.)
2. If ET visit falls in an analysis window which already has non-missing observed value of this parameter from the scheduled visit, ET will be mapped to the next scheduled visit.
3. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.

4. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:
   a. The closest unscheduled visit from the target day will be selected.
   b. If multiple unscheduled visits exist on the same day, the first unscheduled visit will be used.
   c. If the distance is a tie, the unscheduled visit after the target day of the scheduled visit will be used.
5. If mapping distance is greater than 6 weeks, the unscheduled visit will not be mapped.

Unscheduled visits and ET visit will be mapped per the following analysis visit windows based on the study day/visit of each parameter.

Analysis Visit Window for Efficacy Endpoints

Visit from SOE	Target Study Day*	PGIS, SPT for Cat and HDM	RQLQ, Spirometry, ACQ-5 for Asthma patients
Baseline	1	≤1	≤1
Visit 6	85	[2, 253]	[2, 211]
Visit 12	337		[212,379]
Visit 14 (EOT)	421	>253	>379

*Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment ≥1st injection date; otherwise, study day = (date of assessment – 1st injection date). If subject never received any dose of study drug, randomization date will be used in the place of 1st injection date.

Analysis Visit Window for Safety and Biomarkers

Visit from SOE	Target Study Day*	Vital Sign, Drug conc.	Hematology, Blood chemistry	ADA	Serum for sIgE for Fel d 2, 4, and 7	Biomarkers
Baseline	1	≤1	≤1	≤1	≤1	≤1
Visit 6	85	[2, 127]	[2, 127]	[2, 169]	[2, 253]	[2,211]
Visit 8	169	[128, 211]	[128, 211]			
Visit 10	253	[212, 295]	[212, 295]	[170, 295]		
Visit 12	337	[296, 379]	[296, 379]	[296, 379]		[212,379]
Visit 14 (EOT)	421	[380,463]	[380,463]	[380,463]	>253	[380,463]
Visit 15 (EOS)	505	> 463	> 463	> 463		> 463

* Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date + 1) when date of assessment ≥1st injection date; otherwise, study day = (date of assessment – 1st injection date). If subject never received any dose of study drug, randomization date will be used in the place of 1st injection date.
# Post-baseline urinalysis will not be mapping since no scheduled measurements will be collected per protocol.

6.6. Statistical Technical Issues

None.

7. INTERIM ANALYSIS

7.1. Futility Interim Analysis

A non-binding futility interim analysis (IA) in the study is planned to be performed when at least 40% of randomized patients have completed the week 12 visit or discontinued before week 12. There is no plan to change the conduct of this trial except a possibility to stop the trial due to unfavorable benefit-risk. The IA will be performed by independent statisticians that support the IDMC and who are separate from personnel involved in the trial conduct. The IDMC will review the unblinded IA results and recommend action based on the non-binding futility criteria based on CSMS and TNSS that will be specified in Section 7.2.

If the non-binding futility criteria are met, the unblinded results will be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study. Individuals involved in the conduct of the study (i.e., patients, Investigators, Study Team, and Project Team, etc.) will have no access to the IA results.

The analysis population for the interim futility analysis will include at least the first 40% of the randomized patients. An administrative penalty of 0.001 will be taken from the significance level used at final analysis (i.e., 2-sided 0.049 will be used for the final analysis).

7.2. Interim Futility Criteria

Futility will be assessed using criteria based on the following two efficacy endpoints:

- Daily CSMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Daily TNSS, averaged over the initial 12 weeks of treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo

For the IA, the efficacy will be analyzed using the same methods described in the efficacy analyses section (Section 5.6). The least squares means estimates for these two endpoints for each treatment group, as well as the difference between the REGN1908-1909 and placebo will be provided based on an ANCOVA model, with the treatment group, randomization stratification factors (as stratified), and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed effects and the baseline CSMS/TNSS as a covariate. This ANCOVA model as the primary analysis in the study will be conducted for the IA.

Based on these estimates, the standardized effect size and percent reduction in average CSMS and average TNSS for REGN1908-1909 relative to placebo will be calculated. The two steps below will be followed to assess futility:

Step 1: Assess CSMS endpoint. Futility criteria for CSMS will be met if:

a. Mean difference between REGN1908-1909 and placebo is <5%

or

b. Effect size (mean diff./SD) < 0.073*

(* Note: The effect size of 0.073 corresponds to an assumed mean difference in CSMS of 0.455 and a standard deviation of 6.2.)

If neither a. nor b. is met for CSMS, then futility criterion is not met and the study will proceed as planned. If either criteria a. or b. are met, the TNSS endpoint will be evaluated in step 2.

Step 2: Assess TNSS endpoint. Futility criteria for TNSS will be met if:

a. Mean difference between REGN1908-1909 and placebo is <5%

or

b. Effect size (mean diff./SD) < 0.072**

(** Note: The effect size of 0.072 corresponds to an assumed mean difference in TNSS of 0.165 and a standard deviation of 2.3.)

If neither a. nor b. is met for TNSS, then the study will proceed as planned. If either criteria a. or b. are met, the non-binding futility criteria have been met and unblinded results will be reviewed by a small group of senior sponsor individuals.

7.3. Timing of Unblinded Primary Analysis

The unblinded primary analysis may be performed when the last patient completes 60 weeks of treatment duration (or discontinues prior to week 60) in order to expedite the submission to regulatory agencies. No changes in the conduct of the study will be made based on this primary analysis. The assessment of primary and secondary endpoints performed during the analysis will be the final analysis of the primary endpoint and secondary endpoints and 2-sided alpha of 0.049 will be used.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above or using R Version 3.5 or above.

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10. APPENDIX

10.1. Summary of Statistical Analyses

10.1.1. Summary of Efficacy Analyses

Endpoint	Analysis Populations	Primary Analysis	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
Daily CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60)	FAS	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and baseline CSMS as a covariate	Yes - All intercurrent events handled via a treatment policy	Yes	Plot
Secondary Endpoints					
Daily TNSS, TSS, CSMS, TOSS, and DMS over the last 12 and the initial 12 weeks of the efficacy assessment period (weeks 48 to 60, and weeks 0 to 12) and the percent change from baseline in these endpoints (except for daily CSMS over the last 12 weeks)	FAS	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and relevant baseline measurement as a covariate	N/A	Yes	Plot
Percent change from baseline to week 12 cat SPT mean wheal diameter Percent change from baseline to end of treatment (week 60) cat SPT mean wheal diameter Change from baseline to week 60 in RQLQ(S)+12	FAS	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and baseline SPT mean wheal diameter as a covariate	N/A	Yes	Plot
Percent change from baseline to week 12 FEV1 Percent change from baseline to week 60 FEV1 Asthma daily symptom score (ADSS), averaged over the last 12 weeks and the initial 12 weeks of the treatment period (weeks 48-60, weeks 0 to 12) Change from baseline to week 60 in ACQ-5	FAS with asthma	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and relevant baseline measurement as a covariate	N/A	Yes	Plot

10.1.2. Summary of Safety Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	Yes, for selected AE summary	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 6: Schedule of Events

	Screening Period[1]		Randomization	Double-Blind Treatment Period										Follow Up Period		
				Initial Efficacy Assessment								Final (Primary) Efficacy Assessment		End of Treatment (EOT)/ Early Term.	End of Study (EOS)	
Visit	**Screening Visit 1[1]**	**Baseline V2[2]**	**R V3[4]**	**Tel V4**	**Tel V5**	**V6**	**Tel V7**	**V8**	**Tel V9**	**V10**	**Tel V11**	**V12**	**Tel V13**	**EOT V14**	**EOS V15**	**Un-scheduled Visit[13]**
Day	**-85 to -1**		**1**	**8**	**43**	**85**	**127**	**169**	**211**	**253**	**302**	**337**	**365**	**421**	**505**	
Window (day)				**±3**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±7**	**±7**	
Week	**- 12**		**0**	**1**	**6**	**12**	**18**	**24**	**30**	**36**	**43**	**48**	**52**	**60**	**72**	
Screening/Baseline:																
Inclusion/exclusion	X	X	X													
Informed consent/assent	X															
Medical history	X															
Demographics (age, race, height, weight)	X															
Skin prick test for cat and HDM[3]	X[3]					X								X	X	
Skin prick test for other allergens[3]	X[3]															
Dispense e-diary		X										X				
Collect e-diary						X								X		
Dispense rescue meds		X	X			X		X		X		X				
Randomization[4]			X													
Treatment:																
Administer study drug[5]			X			X		X		X		X				
Concomitant meds and treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening Period[1]		Randomization	Double-Blind Treatment Period										Follow Up Period		
				Initial Efficacy Assessment								Final (Primary) Efficacy Assessment		End of Treatment (EOT)/ Early Term.	End of Study (EOS)	
Visit	**Screening Visit 1[1]**	**Baseline V2[2]**	**R V3[4]**	**Tel V4**	**Tel V5**	**V6**	**Tel V7**	**V8**	**Tel V9**	**V10**	**Tel V11**	**V12**	**Tel V13**	**EOT V14**	**EOS V15**	**Un-scheduled Visit[13]**
Day	**-85 to -1**		**1**	**8**	**43**	**85**	**127**	**169**	**211**	**253**	**302**	**337**	**365**	**421**	**505**	
Window (day)				**±3**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±7**	**±7**	
Week	**- 12**		**0**	**1**	**6**	**12**	**18**	**24**	**30**	**36**	**43**	**48**	**52**	**60**	**72**	
Efficacy:																
TNSS, TOSS, DMS		X	Nightly in e-diary									Nightly in e-diary				
PGIS			X			X								X		
PGIC						X										
RQLQ(S)			X			X						X		X		
Evaluation of cat exposure						X		X		X		Daily in e-diary				X
Patient Experience Assessment														X		
Spirometry[6,7]	X[6]		X[6]			X[7]						X[7]		X[7]		
ACQ-5 for asthma patients[7]			X[6]			X[7]						X[7]		X[7]		
ANSD and nighttime awakening for asthma patients[7]		X[7]	Daily in e-diary[7]									Daily in e-diary[7]				
ADSD and asthma rescue med use for asthma patients[7]		X[7]	Nightly in e-diary[7]									Nightly in e-diary[7]				
Safety:																
Vital signs[8]	X	X	X[8]			X[8]		X[8]		X[8]		X[8]		X	X	X
Physical examination	X		X			X		X		X		X		X	X	X
ECG	X															X
Adverse events	X ◄															X

	Screening Period[1]		Randomization	Double-Blind Treatment Period										Follow Up Period		
				Initial Efficacy Assessment								Final (Primary) Efficacy Assessment		End of Treatment (EOT)/ Early Term.	End of Study (EOS)	
Visit	**Screening Visit 1[1]**	**Baseline V2[2]**	**R V3[4]**	**Tel V4**	**Tel V5**	**V6**	**Tel V7**	**V8**	**Tel V9**	**V10**	**Tel V11**	**V12**	**Tel V13**	**EOT V14**	**EOS V15**	**Un-scheduled Visit[13]**
Day	**-85 to -1**		**1**	**8**	**43**	**85**	**127**	**169**	**211**	**253**	**302**	**337**	**365**	**421**	**505**	
Window (day)				**±3**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±7**	**±7**	
Week	**- 12**		**0**	**1**	**6**	**12**	**18**	**24**	**30**	**36**	**43**	**48**	**52**	**60**	**72**	
Laboratory Testing:																
Hematology	X					X		X		X		X		X		X
Blood chemistry	X					X		X		X		X		X		X
Serum pregnancy test for WOCBP	X															X
Urine pregnancy for WOCBP[9]		X	X			X		X		X		X		X		X
FSH test for postmenopausal women only[10]	X															
Urinalysis	X															X
Serum for specific IgE for Fel d 1 and cat	X		X													
Serum for sIgE for Fel d 2, 4, and 7			X			X								X		
Serum for sIgE for other allergens (eg, HDM, etc)	X		X													
PK and ADA:																
Drug conc. sample[11]			X			X		X		X		X		X	X	X
ADA sample[11]			X			X				X		X		X	X	X
Biomarkers:																
Research sample for serum			X			X						X		X	X	X
Research sample for plasma			X			X						X		X	X	X

	Screening Period[1]		Randomization	Double-Blind Treatment Period										Follow Up Period		
				Initial Efficacy Assessment								Final (Primary) Efficacy Assessment		End of Treatment (EOT)/ Early Term.	End of Study (EOS)	
Visit	**Screening Visit 1[1]**	**Baseline V2[2]**	**R V3[4]**	**Tel V4**	**Tel V5**	**V6**	**Tel V7**	**V8**	**Tel V9**	**V10**	**Tel V11**	**V12**	**Tel V13**	**EOT V14**	**EOS V15**	**Un-scheduled Visit[13]**
Day	**-85 to -1**		**1**	**8**	**43**	**85**	**127**	**169**	**211**	**253**	**302**	**337**	**365**	**421**	**505**	
Window (day)				**±3**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±14**	**±7**	**±7**	**±7**	
Week	**- 12**		**0**	**1**	**6**	**12**	**18**	**24**	**30**	**36**	**43**	**48**	**52**	**60**	**72**	
Pharmacogenomics:																
Optional DNA sample (whole blood)[12]			X													
Optional Research Samples: whole blood for RNAseq			X			X						X		X		

Footnotes for the Schedule of Events Table

1. Screening SPT for birch, birch homologous trees, and other common allergens will be performed as described in the study manual. Skin prick test for birch should be performed prior to other screening assessments. If screening SPT for birch is negative (ie, mean wheal diameter <5 mm greater than a negative control), then other screening visit procedures do not need to be performed as the subject will have failed screening (refer to Protocol Section 7.2.1 Inclusion Criteria, #3).
2. Randomization may occur within 1 day prior to study drug administration. All safety assessments performed at screening must be normal and checked against the inclusion/exclusion criteria prior to study drug administration.
3. The timing of in-clinic visits may vary for each study site, depending on the start, peak, and end dates of the local birch pollen season (as determined by local pollen counts; refer to Protocol Section 9.2.2). The randomization visit will be scheduled approximately 2 weeks before the start of birch pollen season, and the end of study (EOS) visit approximately 16 weeks after the randomization visit (depending on the duration of the local birch pollen season). In addition, visit 5 will be scheduled to occur within 2 weeks of the anticipated local peak of the birch pollen season.
4. If randomization occurs >60 days after the screening visit, medical history, blood chemistry, hematology, and spirometry must be repeated prior to randomization.
5. E-diary and rescue medications will be dispensed at the randomization visit. E-diary and any unused rescue medications will be returned at the EOS visit. Refer to Protocol Section 8.2 for more information on rescue treatments.
6. TNSS, TOSS, and DMS will be recorded daily via e-diary, starting at the randomization visit until EOS. Refer to Protocol Section 9.2.4.1, 9.4.2.2 and 9.4.2.4 for procedural details.
7. In asthmatic subjects, ACQ-5 scores will be recorded weekly via e-diary, starting from the randomization visit until EOS. Refer to Protocol Section 9.2.4.6 for procedural details.
8. In all subjects, RQLQ (S) scores will be recorded weekly via e-diary starting from the randomization visit until EOS. Refer to Protocol Section 9.2.4.7 for procedural details. In asthmatic subjects, the weekly RQLQ (S) and ACQ-5 assessments may be performed on the same day.
9. Refer to for Protocol Section 9.2.4.8 procedural details.
10. Refer to for Protocol Section 9.2.4.9 procedural details.
11. Vital signs include systolic and diastolic blood pressure, respiratory rate, and heart rate. Vital signs will be collected in a seated position. At the randomization visit, vital signs are taken prior to PK blood draw, prior to study drug administration, and at 2 hours (±10 min) after completion of the injection.
12. A full physical exam must be performed at screening, at baseline, and at EOS. A limited physical exam will be done at remaining visits depending on presentation of the subject.

13. If the urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation. At the randomization visit, if a serum pregnancy test must be performed, study drug cannot be administered unless the serum pregnancy test is negative. Urine pregnancy test can be performed on day -1 of the visit at the investigator's discretion.
14. **At-home pregnancy testing:** WOCBP will be provided with urine pregnancy tests for at-home testing prior to visits 4 and 6. Study sites will collect the results by telephone at these visits. If the urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
15. PK and ADA samples are to be collected prior to study drug administration. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional samples for PK and ADA analyses may be collected as close to the event as practically possible.
16. Refer to Protocol Section 9.2.11.
17. Genomic analysis is optional for all subjects enrolling in the study. One DNA sample is to be collected at the randomization visit, but if this sample collection was omitted at baseline, it can be collected at any subsequent visit. Refer to Protocol Section 9.2.12.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
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	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.	>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.	>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
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	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.	>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.	>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
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.	≥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.	>1.5 ULN [≥1.5 ULN] and baseline ≤ 1.5 ULN [<1.5 ULN]

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
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. Concept paper on DILI – FDA draft Guidance Oct 2007.	≥1.3 ULN and baseline < 1.3 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Based on normal range: <1 mg/dL, CF = mg x 1.7 = µmol Concept paper on DILI – FDA draft Guidance Oct 2007. Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN (adults only) >2 ULN [≥1.3 ULN] and baseline ≤ 2.0 ULN [<1.3 ULN]
(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.	((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.	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and baseline ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN))
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	≥132µmol/L and baseline < 132µmol/L (or ≥1.5 mg/dL and baseline <1.5 mg/dL) ≥30% change from baseline	Benichou C., 1994. 3 independent criteria	>150 [≥132] µmol/L and baseline < 150 [<132] µmol/L ≥30% change from baseline and <100% change from baseline ≥100% change from baseline

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
Uric Acid	<120 µmol/L and ≥ 120 µmol/L at baseline >408 µmol/Land ≤ 408 µmol/L at baseline	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria	≤2 mg/dL and >2 mg/dL at baseline (or ≤119 µmol/L and baseline >119 µmol/L) >8.0 mg/dL and ≤8.0 mg/dL at baseline (or >476 µmol/L and ≤476 µmol/L at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008. Two independent criteria	>408 [>476] µmol/L and ≤408 [≤476] µmol/L at baseline <120 µmol/L and ≥120 µmol/L at baseline
Blood Urea Nitrogen (BUN)	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria	≥20 mg/dL and <20 mg/dL at baseline (or ≥7.14 mmol/L and <7.14 mmol/L at baseline)		≥17 [≥7.14] mmol/L and <17 [<7.14] mmol/L at baseline
Calcium			<2 mmol/L and baseline ≥2 mmol/L (or ≤ 8 mg/dL and baseline >8 mg/dL) ≥2.9 mmol/L and baseline <2.9 mmol/L (or ≥11.6 mg/dL and baseline <11.6 mg/dL)		<2 mmol/L and baseline ≥2 mmol/L (or ≤ 8 mg/dL and baseline >8 mg/dL) ≥2.9 mmol/L and baseline <2.9 mmol/L (or ≥11.6 mg/dL and baseline <11.6 mg/dL) (adolescents only)
Chloride	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤115 mmol/L	Two independent criteria	<80 mmol/L and baseline ≥80 mmol/L ≥115 mmol/L and baseline < 115 mmol/L		<80 mmol/L and baseline ≥80 mmol/L >115 [≥115] mmol/Land baseline ≤ 115 [< 115] mmol/L

Parameter	**Adults**	**Comments for adults**	**Adolescents (≥12 to <18)**	**Comments for adolescents**	**Combined**
Sodium	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline < 160 mmol/L	Two independent criteria	<129 mmol/L and baseline ≥ 129 mmol/L ≥150 mmol/L and baseline <150 mmol/L	Two independent criteria Reference ranges are same in adolescents (12-17 yrs. old) and adults	≤129 [<129] mmol/L and baseline > 129 [≥129] mmol/L ≥160 [≥150] mmol/L and baseline <160 [<150] mmol/L
Potassium	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline < 5.5 mmol/L	FDA Feb 2005. Two independent criteria	≤3.5 mmol/L and baseline >3.5 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	FDA Feb 2005. Two independent criteria	<3 [≤3.5] mmol/L and baseline ≥ 3 [>3.5] mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L
Glucose	Hypoglycaemia: (≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or ≥LLN) at baseline Hyperglycaemia: >=7 mmol/L (fasted) and <7 mmol/L at baseline (fasted); >=11.1 mmol/L (unfasted) and <11.1 mmol/L at baseline (unfasted)	ADA Jan 2008.	<2.7 mmol/L and ≥2.7 mmol/L at baseline (or < 50 mg/dL and ≥ 50 mg/dL at baseline) ≥10 mmol/L (unfasted) and < 10 mmol/L (unfasted) at baseline (or ≥180 mg/dl and <180 mg/dl at baseline); ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline (or ≥120 mg/dL and <120 mg/dL at baseline)		(≤3.9 [<2.7] mmol/L and <LLN) and (>3.9 [≥2.7] mmol/L or >=LLN) at baseline ≥11.1 [≥10] mmol/L (unfasted) and <11.1 [<10] mmol/L (unfasted) at baseline; ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline
Albumin	≤25 g/L and >25 g/L at baseline		≤25 g/L and >25 g/L at baseline	Reference ranges are same in children (6-17 yrs. old) and adults	≤25 g/L and >25 g/L at baseline

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
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) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline		<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) [<4.0 Giga/L and ≥4.0 Giga/L at baseline] ≥16.0 [>13.5] Giga/L and < 16 [≤13.5] Giga/L at baseline
Lymphocytes (ALC)	>4.0 Giga/L and ≤4.0 Giga/L at baseline		<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline		<0.6 Giga/L and ≥0.6 Giga/L at baseline (adolescents only) >4.0 [>6.0] Giga/L and ≤4.0 [≤6.0] Giga/L at baseline
Neutrophils	<1.5 Giga/L and ≥1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and ≥1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN		<1.5 Giga/L and ≥1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and ≥1.0 Giga/L at baseline (Black) [<1.2 Giga/L and ≥1.2 Giga/L at baseline] >ULN and baseline ≤ ULN (adolescents only)
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline		>1.2 Giga/L and <= 1.2 Giga/L at baseline		>0.7 [>1.2] Giga/L <= 0.7 [≤1.2] Giga/L at baseline

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
Basophils	>0.1 Giga/L and ≤ 0.1 Giga/L at baseline		>0.2 Giga/L		>0.1 Giga/L and ≤ 0.1 Giga/L at baseline [>0.2 Giga/L]
Eosinophils	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of Internal Medicine 17th Ed., 2008.	(>0.5 Giga/L and >ULN) and (≤ 0.5 Giga/L or ≤ ULN at baseline)	Harrison- Principles of internal Medicine 17th Ed., 2008.	(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ULN at baseline)
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. 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).	<100 g/L and ≥100 g/L at baseline (or <10 g/dL and >10 g/dL at baseline) ≥200 g/L and <200 g/L at baseline (or ≥20 g/dL and <20 g/dL at baseline) Decrease from Baseline ≥20 g/L	Two criteria are independent	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. [<100 g/L and ≥100 g/L at baseline] ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female [≥200 g/L and <200 g/L at baseline] 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 for Female ≥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 *The default criteria. By gender (male and female) are optional.	<0.37 v/v and ≥ 0.37 v/v at baseline for Male ; <0.33 v/v and ≥0.33 v/v at baseline for Female >0.52 v/v and ≤0.52 v/v at baseline for Male ; >0.47 v/v and ≤0.47 v/v at baseline for Female	Two criteria are independent	≤0.37 [<0.37] v/v and > 0.37 [≥ 0.37] v/v at baseline for Male ; ≤0.32 [<0.33] v/v and > 0.32 [≥0.33] v/v at baseline for Female ≥0.55 [>0.52] v/v and < 0.55 [≤0.52] v/v at baseline for Male ; ≥0.5 [>0.47] v/v and < 0.5 [≤0.47] v/v at baseline for Female

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
RBC	<4 Tera/L and ≥ 4 Tera/L at baseline for Male ; <3 Tera/L and ≥ 3 Tera/L at baseline for Female ≥7 Tera/L and <7 Tera/L at baseline for Male ; ≥6 Tera/L and <6 Tera/L at baseline for Female	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.	NONE		<4 Tera/L and ≥ 4 Tera/L at baseline for Male ; <3 Tera/L and ≥ 3 Tera/L at baseline for Female ≥7 Tera/L and <7 Tera/L at baseline for Male ; ≥6 Tera/L and <6 Tera/L at baseline for Female (adults only)
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	<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	<100 Giga/L and ≥ 100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline
Vital signs					
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm		≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm		≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg		Hypotension: SBP ≤90 mmHg; and decrease from baseline ≥20 mmHg Hypertension: ≥119 mmHg; and increase from baseline ≥20 mmHg	Based on definition of hypotension as SBP<5th percentile for gender, age and height Based on definition of Hypertension as average SBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions	≤95 [≤90] mmHg and decrease from baseline ≥20 mmHg ≥160 [≥119] mmHg and increase from baseline ≥20 mmHg

Parameter	Adults	Comments for adults	Adolescents (≥12 to <18)	Comments for adolescents	Combined
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg		Hypotension: DBP ≤54 mmHg and decrease from baseline ≥10 mmHg Hypertension: ≥78 mmHg and increase from baseline ≥10 mmHg	Based on definition of Hypertension as average DBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions	≤45 [≤54] mmHg and decrease from baseline ≥10 mmHg ≥110 [≥78] mmHg and increase from baseline ≥10 mmHg
Respiratory rate	< 12 per minutes and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline		<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline		<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline

10.4. Search Criteria for TEAE of Special Interest

AESI	Search Criteria
Systemic or severe hypersensitivity reactions	Narrow SMQ for hypersensitivity Anaphylaxis will be prospectively analysised as follows: 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
Asthma exacerbations	Asthma symptoms (based on narrow SMQ for asthma) requiring treatment with systemic corticosteroids or resulting in an emergency room visit or hospitalization.

10.5. Prohibited Medications Relevant for Analysis

Prohibited medications as defined in Section 4.4 have been further categorized into groups based on their expected impact on the efficacy variables and planned data handling method:

- **Category 1** – Medications that are not expected to impact efficacy variables (treatment policy)
- **Category 2** – Medications that require blinded adjudication (considering factors such as the type of medication, indication, timing, and frequency) to determine if data should be handled by treatment policy, composite strategy (in the case of medications that are expected to impact efficacy variables and may be indiciative of treatment failure), or hypothetical strategy (in the case of medications that are expected to impact efficacy variables but are not indicative of treatment failure)
- **Category 3** – Medications that are expected to impact efficacy variables, but are not indicative of treatment failure (hypothethical strategy)

These categories have been defined separately for the following groups of endpoints:

- CSMS, TNSS, TOSS, DMS and RQLQ(S)+12 endpoints (Table 7)
- Asthma-related endpoints (Table 8)
- SPT endpoints (Table 9)

Table 7: Prohibited medication categories for CSMS, TNSS, TOSS, DMS and RQLQ(S)+12 endpoints

Category 1	**Category 2**
Treatment policy	**Adjudication to determine treatment policy, composite strategy, or hypothetical strategy**
1st gen, 2nd gen oral antihistamines/ intranasal antihistamines/ ocular antihistamines	Corticosteroids (intra-muscular/ intra-articular/ extended duration implants such as intravitreal etc)
Longer acting antihistamines (eg, Hydroxyzine/ Cyproheptadine)	Oral/ IV corticosteroids
Topical/ oral decongestants	Systemic calcineurin inhibitors
Intranasal anticholinergics	SIT with any allergen other than cat
	Immune directed biologics and/or therapies that would interfere with Type 2 allergic disease or suppress the immune system, including but not limited to anti-IgE, anti IL-5, anti Il-4
	Specific immunotherapy (SIT) with cat allergen or vaccines against cat allergy
Intranasal corticosteroids	
Ocular corticosteroids	
Ocular/intranasal cromoglycates	
Methylxanthines	
Leukotreine modifiers	

Table 8: Prohibited medication categories for asthma-related endpoints

Category 1 **Treatment policy**	**Category 2** **Adjudication to determine Treatment Policy, Composite Strategy, or Hypothetical Strategy**	**Category 3** **Hypothetical Strategy (Multiple Imputation)**
1st gen, 2nd gen oral antihistamines/ intranasal antihistamines/ ocular antihistamines	Corticosteroids (intra-muscular/ intra-articular/ extended duration implants such as intravitreal etc)	Inhalational Corticosteroids, SABA/LABA/LAMA if not washed out within timeframes specified in the study protocol
Longer acting antihistamines (eg, Hydroxyzine/ Cyproheptadine)	Oral/ IV corticosteroids	
Topical/ oral decongestants	Immune directed biologics and/or therapies that would interfere with Type 2 allergic disease or suppress the immune system, including but not limited to anti-IgE, anti IL-5, anti Il-4	
Intranasal anticholinergics	Specific immunotherapy (SIT) with cat allergen or vaccines against cat allergy	
Intranasal corticosteroids		
Ocular corticosteroids		
Ocular/intranasal cromoglycates		
Methylxanthines		
Leukotreine modifiers		

Table 9: Prohibited medication categories for SPT endpoints

Category 1 **Treatment policy**	**Category 2** **Adjudication to determine Treatment Policy, Composite Strategy or Hypothetical Strategy**	**Category 3** **Hypothetical Strategy (Multiple Imputation)**
1st gen, 2nd gen intranasal antihistamines/ ocular antihistamines	Immune directed biologics and/or therapies that would interfere with Type 2 allergic disease or suppress the immune system, including but not limited to anti-IgE, anti IL-5, anti Il-4	1st gen, 2nd gen oral antihistamines (5 day window)
Topical/ oral decongestants	Specific immunotherapy (SIT) with cat allergen or vaccines against cat allergy	Longer acting antihistamines (eg, Hydroxyzine/ Cyproheptadine) (10 day window)
Intranasal anticholinergics		
Intranasal corticosteroids		
Ocular corticosteroids		
Ocular/intranasal cromoglycates		
Methylxanthines		
Leukotreine modifiers		
Corticosteroids (intra-muscular/ intra-articular/ extended duration implants such as intravitreal etc)		
Oral/ IV corticosteroids		
Systemic calcineurin inhibitors		
SIT with any allergen other than cat		

10.6. Additional Details on Sample Size Adjustment

The table below provides power and sample size calculations based on various observed values of standard deviation of CSMS and TNSS. These calculations may be used as a guide if a sample size adjustment is deemed necessary.

Endpoint (mean in protocol)	Observed SD (% of the SD in protocol)	Effect size	Power with current planned sample size*±	Sample size [% increase from protocol] required for 90% power*¥
CSMS (9.1)	6.2 (as assumed in protocol)	0.293	90%	315 [as assumed in protocol]
	6.5 (4.8% increase)	0.280	87%	346 [10%]
	6.8 (10% increase)	0.267	83%	379 [20.3%]
	7.1 (15% increase)	0.256	80%	413 [31.1%]
	7.4 (20% increase)	0.246	77%	449 [42.5%]
TNSS (3.3)	2.3 (as assumed in protocol)	0.29	89%	323 [2.5%]
	2.4 (4.3% increase)	0.28	86%	346 [10%]
	2.5 (10% increase)	0.26	83%	382 [21.3%]
	2.65 (15% increase)	0.25	79%	428 [35.9%]
	2.8 (20% increase)	0.24	74%	478 [51.7%]

*: Two-sided t-test with alpha = 0.049, assuming 20% reduction from PBO (mean difference = 1.8 for CSMS and 0.66 for TNSS)
±: Power assuming sample size = 251/arm (assuming 315/arm are enrolled and a 20% dropout rate)
¥: Sample size is inflated to account for a 20% drop-out rate

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