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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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

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LIST OF ABBREVIATIONS AND DEFINITIONS 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)
CRO	Contract research organization
CSMS	Combined symptom and medication score
DMS	Daily medication score
EAR	Early asthmatic response
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EEU	Environmental exposure unit
FAS	Full analysis set
FBR	Future biomedical research
FDA	United States Food and Drug Administration
Fel d 1	*Felis domesticus* allergen 1
GCP	Good Clinical Practice
GINA	Global Imitative for Asthma
GPS	Global Patient Safety
HDM	House dust mite
HRQoL	Health related quality of life
IA	Interim analysis
IAF	Informed assent form
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IgE	Immunoglobulin E
INCS	Intranasal corticosteroids
IRB	Institutional Review Board
LABA	Long-acting beta 2-agonist
LAMA	Long-acting muscarinic antagonist
mAb	Monoclonal antibody
NAb	Neutralizing antibody
pERK	Phosphorylated extracellular signal-regulated kinase
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.
RBQM	Risk-Based Quality Monitoring
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire for Ages 12+
SABA	Short-acting beta 2-agonist
SAE	Serious adverse event
SAF	Safety analysis set
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SIT	Specific immunotherapy
SOC	System organ class
SPT	Skin prick test
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
TSS	Total symptom score
WBC	White blood cell

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AMENDMENT HISTORY

Amendment 3

Note: Amendment 2 was a country-specific amendment. Amendment 3 is a global amendment. All changes made in Amendment 2 are implemented globally in Amendment 3.

The main purpose of this amendment is to add safety assessments and to change the timing of the primary efficacy endpoint assessment from the initial to the last 12 weeks of the treatment period, per health authority requests. Instructions for the skin prick test were modified to ensure that this measurement of efficacy is performed in a manner to prevent accidental unblinding starting during the treatment period. In countries where local regulations or approvals permit enrollment of adults only, enrollment was restricted to patients who are ≥18 years of age. The percent change from baseline in daily combined symptom and medication score (CSMS) and symptom scores, averaged over the initial 12 weeks (weeks 0 to 12) and the last 12 weeks (weeks 48 to 60) of the treatment period, in patients who receive REGN1908-1909 versus placebo, were added as secondary endpoints. A non-binding interim futility analysis will now be performed when at least 40% of randomized patients have completed the week 12 visit or discontinued before week 12. Other, more minor changes were also implemented.

The following table outlines the changes made to the protocol and the rationale.

Description of Change	Brief Rationale	Sections Changed
The following safety assessments were added as study procedures: • Physical examination will now also be performed at the week 24 and 36 visits • Samples for hematology and blood chemistry will now also be collected at the week 24, 36, and 48 visits	Additional safety assessments were added per Health Authority request.	Table 3: Schedule of Events
The timing of the primary efficacy assessment period was changed such that the daily CSMS will be averaged over the last 12 weeks of the treatment period (weeks 48 to 60) instead of the initial 12 weeks of the treatment period (weeks 0 to 12) in patients who received REGN1908-1909 versus placebo. The analysis of the daily CSMS averaged over the initial 12 weeks of the treatment period (weeks 0 to 12) will now be considered a secondary efficacy endpoint.	Per health authority suggestion, the timing of the primary endpoint was changed in acknowledgement that REGN1908-1909 is proposed as a chronic therapy.	Clinical Study Protocol Synopsis, Primary Endpoint Clinical Study Protocol Synopsis, Secondary Endpoints Clinical Study Protocol Synopsis, Statistical Plan Section 3.1 Hypotheses Section 3.2.1 Rationale for Study Design Section 4.1 Primary Endpoint Section 4.2 Secondary Endpoints Section 6.1 Study Description and Duration Table 2: Medications Prohibited During Specific Periods of the Study Figure 1: Study Flow Diagram

Description of Change	Brief Rationale	Sections Changed
		Table 3: Schedule of Events Section 9.1.2 Early Termination Visit Section 11.1 Statistical Hypothesis Section 11.4.3.1 Primary Efficacy Analysis Table 5: Summary of Estimand for Primary Endpoint
In addition to changing the primary endpoint timing, other endpoints under "key secondary," "other secondary," and "exploratory" were re-categorized.	Categorization of endpoints was reconsidered based on the change in timing for the primary endpoint and to more accurately reflect the analyses intended by the sponsor.	Clinical Study Protocol Synopsis, Primary Endpoint Clinical Study Protocol Synopsis, Secondary Endpoints Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints
The percent change from baseline in daily combined symptom and medication score (CSMS) and symptom scores, averaged over the initial 12 weeks (weeks 0 to 12) and last weeks (weeks 48 to 60) of the treatment period in patients who receive REGN1908-1909 versus placebo were added as secondary endpoints.	The daily CSMS, averaged over the last 12 weeks of the treatment period in patients who receive REGN1908-1909 versus placebo is the primary endpoint of the study and symptom and medication scores analyzed in a similar manner are secondary endpoints during weeks 0 to12 and weeks 48 to 60 in the current protocol; the percent change from pre-treatment baseline in these parameters were added as secondary endpoints.	Clinical Study Protocol Synopsis, Secondary Endpoints Clinical Study Protocol Synopsis, Statistical Plan Section 4.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Table 6: Summary of Estimands for Key Secondary Endpoints and Select Other Secondary Endpoint
Percent change from pre-treatment baseline over the initial 12 weeks and the last 12 weeks of the treatment period in patients with asthma who receive REGN1908-1909 versus placebo for average asthma daily symptom score (ADS), average frequency of asthma rescue medication use, and average frequency in nighttime awakenings will be analyzed as exploratory endpoints.	The data for these analyses will be collected and percent change in these parameters from pre-treatment baseline over the initial 12 weeks and the last 12 weeks of the treatment period can analyzed for exploratory research.	Clinical Study Protocol Synopsis, Other Secondary Endpoints Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints
Instructions for the skin prick test (SPT) post-randomization were modified to ensure that this measurement of efficacy is performed in a manner to prevent accidental unblinding starting during the treatment period. The SPTs (cat, saline, histamine, and house dust mites) will be run in replicate (8 total) with a blinded code. The allergen wells will be blinded by the unblinded	The anti-Fel d 1 antibodies suppress SPT based on the mechanism of action of the drug by binding to the allergen and inhibition of type I, immediate, IgE-mediated response. A blinding strategy for the skin prick test was added to ensure the integrity of the clinical study results by preventing accidental unblinding in some	Table 3: Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, footnote #3 Section 9.2.2.9 Skin Prick Test

Description of Change	Brief Rationale	Sections Changed
pharmacist (or qualified designee) and provided with labels (allergen #1 to allergen #7) to the blinded personnel. One positive control histamine skin prick test will not be blinded. House dust mite SPT will be added at weeks 12, 60, and 72 to be performed with the cat SPT testing.	patients that may have a large suppression of SPT to cat allergen. Patients with allergic rhinitis are frequently poly-allergic and symptoms due to house dust mite allergy could potentially overlap during the efficacy assessment periods for the study. Therefore, house dust mite SPT has been added at additional timepoints during the study due to the longer trial duration to identify any new sensitizations that may potentially impact efficacy and to help maintain the blind for the cat SPT.	
Eligibility criteria were modified to specify that for those countries where local regulations or approvals permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age.* Additional language to further support the rationale for inclusion of adolescents was added to Rationale for Study Design.	These modifications were made to accommodate local regulations or approvals in countries where enrollment of adolescents was not permitted.	Clinical Study Protocol Synopsis, Study Design Clinical Study Protocol Synopsis, Target Population Clinical Study Protocol Synopsis, Sample Size Section 3.2.1 Rationale for Study Design Section 6.1 Study Description and Duration Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #1
A non-binding interim futility analysis will be performed when at least 40% of randomized patients have completed the week 12 visit or discontinued before week 12. The details of the analysis will be described in the Statistical Analysis Plan.	The results of the interim futility analysis will inform internal business decisions regarding this study and the clinical development program.	Clinical Study Protocol Synopsis, Control of Multiplicity Section 6.2 Planned Interim Analysis Section 6.3.1 Independent Data Monitoring Committee Section 11.4.4 Control of Multiplicity Section 11.4.5 Timing of Statistical Analyses
Text was added to clarify that in-class equivalents of the protocol-specified rescue medications may be used, if discussed and agreed upon with the sponsor.	This clarification was made to allow flexibility regarding rescue medication.	Section 8.2 Rescue Treatments Section 8.9.2 Permitted Medications Section 9.2.2.4 Daily Medication Score
Additional criteria were added for permanent and temporary discontinuation of study drug.	The safety precaution for asthmatic patients was added to the criteria for permanent study drug discontinuation per Ethics	Section 8.3.2.1 Reasons for Permanent Discontinuation of Study Drug

Permanent Discontinuation • A serious or severe asthma event deemed related to study drug that in the opinion of the investigator would result in an increased risk to the patient or a ≥50% decline in FEV1 from pre-treatment baseline. • If, in the investigator's opinion or at the specific request of the sponsor, continuation of study drug would be detrimental to the patient's well-being, there is no longer any potential for benefit, or if continuation would undermine the scientific integrity of the study • In the event of a critical protocol deviation, at the discretion of the investigator or the sponsor Temporary Discontinuation • An asthmatic patient experiencing an asthma exacerbation and/or a clinically relevant decrease in FEV1 ≥20% below baseline at a visit during which study drug was scheduled to be dosed, per investigator judgement. In this case, the patient may return to the clinic within the dosing visit window to be re-assessed for eligibility to receive study drug. • Other intercurrent illness or adverse event or major surgery that could, in the opinion of the investigator, present an unreasonable	Committee (EC) and regulatory agency recommendation. The additional criteria for permanent or temporary study drug discontinuation were added to prevent administration of study drug when not advisable. The increased window for study drug dosing allows patients additional time to avoid missed doses.	Section 8.3.2.2 Reasons for Temporary Discontinuation of Study Drug Changes pertaining to increased dosing window: Section 9.1.1 Footnotes for the Schedule of Events, footnote #6 Section 9.2.2.10 Spirometry Table 3: Schedule of Events

Description of Change	Brief Rationale	Sections Changed
risk to the patient as a result of his/her continued use of the study drug To avoid redundancy with the newly added criterion, "surgical procedure" was removed from the Temporary Discontinuation list. To accommodate the increased window for study drug administration, the dosing visit windows for visits during which study drug is scheduled to be administered was changed from ±7 to ±14 days.		
A statement was added to further clarify that specific asthma medications - bronchodilators (beta-agonists and muscarinic antagonists) - will be washed out prior to spirometry assessments to prevent interference with spirometry and the recommended washout periods. Washout for bronchodilators was removed from the Medications Prohibited During Specific Periods of the Study table and added to the study procedures section describing spirometry with examples of washout timeframes (less restrictive).	This text was added to ensure accurate spirometry results and to ensure patient safety, EC recommendation.	Table 2: Medications Prohibited During Specific Periods of the Study Section 9.2.2.10 Spirometry
Modifications and clarifications were made to prohibited medications. Modifications include the following: • Systemic calcineurin inhibitors were added as medications prohibited prior to screening and throughout the study. Topical calcineurin inhibitors have been removed from the list of prohibited medications • Decongestants are now prohibited from the baseline assessment period up to week 12 and from weeks 48 to 60 with a 3-day washout period. Previously there was no restriction on the use of decongestants. General clarification was added that anti-allergic medications (such as antihistamines, anti-allergic eye drops,	These medications may impact efficacy endpoint measurements.	Table 1: Medications Prohibited Prior to Screening and Throughout the Study Table 2: Medications Prohibited During Specific Periods of the Study

Description of Change	Brief Rationale	Sections Changed
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).		
Eligibility criteria were modified to exclude participation of any patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.	This exclusion criterion is an addition to the sponsor's protocol template aimed to increase the ethical integrity of clinical studies.	Section 7.2.2 Exclusion Criteria, criterion #27
Language was added to clarify that the total rhinitis/conjunctivitis symptom score is based on total symptom score (TSS), which will be measured to determine whether a patient has a daily total rhinitis/conjunctivitis symptom score of at least 8 of 18 during at least 8 days of the 15-day baseline assessment period.	Clarification was added per Health Authority suggestion.	Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criterion #5
Language was added to clarify that whether a patient has significant multiple and/or severe allergies is to be assessed by the investigator in the criterion excluding patients from study participation who have a history of significant multiple and/or severe allergies that would potentially interfere with the assessments during the baseline and 12-week efficacy assessment periods or confound results.	This clarification was made per health authority suggestion.	Section 7.2.2 Exclusion Criteria, criterion #1
Text was added to specify that if, during the screening period, missing data are reported due to documented e-diary malfunction (eg, technical issues that are reported to the vendor), then the baseline assessment period may be extended accordingly, allowing the 15-day period to be re-started, to ensure that a consecutive 15-day period can be obtained. In such a circumstance, the medical monitor should be consulted, and agreement must be obtained with the sponsor.	This was added to ensure that otherwise eligible patients are not deemed ineligible for study participation due to technical issues that may arise with e-diary usage.	Section 6.1 Study Description and Duration Section 9.1.1 Footnotes for the Schedule of Events, footnote #2
Text was added specifically to state the in-clinic observation period of 2 hours post-drug administration after each dose of study drug.*	More specific text was added for clarity surrounding the in-clinic observation period that is in place to ensure patient safety, per EC and Health Authority recommendation.	Table 3: Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events, footnote #5 (added; subsequent footnotes were re-numbered accordingly)
The number of vital sign measurements to be performed was clarified and vital	These changes clarify the number of vital sign measurements to be performed. Additional vital sign	Section 9.1.1 Footnotes for the Schedule of Events, footnote #8

Description of Change	Brief Rationale	Sections Changed
sign measurements were added post drug administration on visits 6 and 12.	measurements added for patient safety, per Health Authority recommendation.	
In addition to the current evaluation of cat exposure at the screening, baseline, and randomization visits (via the inclusion/exclusion criteria), patients will now also be asked about their exposure to cat(s) at study visits 6, 8, 10, 12, 14, and at any unscheduled visit.* In addition, from week 48 through week 60, as part of the patient reported e-diary, patients will be asked to report exposure to their cat(s).	These questions are important to understand a patient's continued exposure to cat(s), per Health Authority recommendation.	Clinical Study Protocol Synopsis, Procedures and Assessments Table 3: Schedule of Events Section 9.2.2.11 Evaluation of Cat Exposure
Patients will answer questions (Patient Experience Assessment) at end of treatment (week 60) to assess changes that patients experienced over the course of the study regarding the amount of time they spent with their cat(s) and the impact on their health status.	These changes may support assessment of impact of drug on efficacy outcomes.	Clinical Study Protocol Synopsis, Procedures and Assessments Table 3: Schedule of Events Section 9.2.2.11 Patient Experience Assessment
Patients with comorbid asthma will now complete the Asthma Daytime Symptom Diary (ADSD), questions on asthma rescue medication use, the Asthma Nighttime Symptom Diary (ANSD) and questions on nighttime awakening during the last 12 weeks of the treatment period (weeks 48 to 60), in addition to the previously specified timeframe of weeks 0 to 12.	This change allows the efficacy analyses for patients with asthma to be performed during the primary efficacy analysis period.	Section 3.2.1 Rationale for Study Design Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 6.1 Study Description and Duration Table 3: Schedule of Events
Instructions for the body weight assessment that specified that patients should void (empty bladder) prior to weight assessment and that patients should be wearing undergarments only and no shoes during the weight assessment were removed.	This change allows flexibility for performing this assessment, per feasibility at each study site.	Section 9.2.4.1 Body Weight
A statement was added to allow sample size re-estimation in a blinded fashion after greater than 50% of patients have baseline data available using observed values of CSMS to determine the baseline PBO 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.	This will ensure adequate sample size for the planned analyses.	Clinical Study Protocol Synopsis, Justification of Sample Size Section 11.2 Justification of Sample Size Table 4: Summary of Statistical Assumptions and Power for Selected Secondary Endpoints
Modifications and clarifications were made specifying how to handle the	The composite approach allows the analysis to include observed values	Section 11.4.3.1

Description of Change	Brief Rationale	Sections Changed
intercurrent event of prohibited medications. The primary estimand for the relevant prohibited medications will utilize the observed TNSS, TOSS, and DMS prior to receiving prohibited medication or the worst score of all observations in corresponding treatment group if a patient has no single value of CSMS during the 12-week assessment period (composite strategy) to handle intercurrent events. Previously, a hypothetic strategy was proposed.	prior to receiving prohibited medications.	Primary Efficacy Analysis Table 5: Summary of Estimand for Primary Endpoint Table 6: Summary of Estimands for Key Secondary Endpoints and Select Other Secondary Endpoint
A modification was made to specify that the worst score to impute the missing data should be the worst one of the observations in the corresponding treatment group if a patient does not have any observed value of the endpoint during the 12-week assessment period because of the patients' discontinuation from study due to AEs and lack of efficacy.	The change supports the imputation considering treatment groups.	Section 11.4.3.1 Primary Efficacy Analysis Table 5: Summary of Estimands for Primary Endpoint Table 6: Summary of Estimands for Key Secondary Endpoints and Select Other Secondary Endpoint
Language was added specifying that if a pregnancy occurs during the study, information about the progress and outcome of the pregnancy will be collected. This should include the date that the subject became pregnant, information about the health of the subject, any medication treatments received during the pregnancy, any medical problems affecting or related to the pregnancy and/or the baby, whether the pregnancy came to term, the date of the child's birth, and the health of the child after birth. To collect this information, the study staff should contact the subject every trimester for updates on the pregnancy. The subject should also be asked to contact the site as soon as possible in the event of any medical problem affecting or related to the pregnancy and/or baby. Once the baby is born, the study staff will ask for a final update after one well-baby visit with the pediatrician.	More specific instructions were added regarding the collection of information related to a pregnancy in order to standardize the type of information collected.	Section 10.1.1 General Guidelines
A statement was added noting that anaphylaxis will be prospectively analyzed using the criteria discussed in the statement paper from the Second	This statement and reference were added based on health authority suggestion.	Section 10.1.3 Events that Require Expedited Reporting to the Sponsor

Description of Change	Brief Rationale	Sections Changed
Symposium on the definition and Management of Anaphylaxis (Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97).		
Exclusion criterion number 13 was modified to "SIT with any allergen other than cat at screening visit 1. Patients who plan to initiate SIT during the trial period will be excluded." The prior criterion excluded patients on SIT with any allergen other than cat within 6 months prior to screening visit 1.	This change was made to allow more flexibility for patients to enroll in the trial if they were not on allergen specific immunotherapy other than cat at screening visit 1 without the requirement for a 6-month washout prior to screening, based on health authority feedback.	Section 7.2.2 Exclusion Criteria, criterion #13
Treatment-emergent adverse events (TEAEs) will be 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.	This definition within the safety analysis section was updated to align with the endpoints.	Section 11.4.6.1 Adverse Events
The 3 locations for subcutaneous (SC) injection (upper arms, abdomen, and thighs) for a single dose was added to the description of investigational treatments, along with the recommendation not to administer all 3 injections in the same site. A statement that there will be 5 visits during the treatment period during which study drug will be administered for a total of 15 injections was also added.	Additional instructional and descriptive information regarding study drug administration was provided in the protocol for convenience and clarity.	Section 8.1 Investigational and Reference Treatments
Text was added to clarify that treatment of cat allergy includes removal of the cat from the home and that this study is intended for those who continue to have cat exposure in the home. Additionally, text was added to support the persistence of cat allergen even after removal of a cat from the home.	These modification were added per EC request and to support that treatment of cat allergy can be challenging in patients who continue to have cat allergen exposure.	Section 1 Introduction Section 3.3 Risk-Benefit
Clarification of clinical pharmacology data for study dosing was added to support multiple administration.	Additional text was added to support the study drug dosing for this study.	Section 3.2.2 Rationale for Dose Selection
Instructions consistent with the sponsor's latest guidelines for receipt of a COVID-19 vaccine (initial series or booster) by a study participant during the study were added.	The sponsor has issued guidance on receipt of the COVID-19 vaccine in relation to the conduct of its clinical studies.	Section 8.9.2 Permitted Medications

Description of Change	Brief Rationale	Sections Changed
The statement that shift tables based on baseline normal/abnormal and other tabular graphical methods may be used to present the results for laboratory tests of interest was removed from the protocol.	Analysis and presentation of these data will be discussed, as relevant, in the Statistical Analysis Plan.	Section 11.4.6.2 Other Safety
Minor editorial changes, clarifications, and updates to align with the current sponsor template were made.	These changes were made to increase clarity and improve readability.	Throughout the protocol.
*Note that this change was implemented in the country-specific protocol amendment 2.		

Amendment 2 DE

Amendment 2 was a country-specific amendment. All changes made in Amendment 2 were implemented globally in Amendment 3.

Amendment 1

The purpose of this protocol amendment is to correct a typo and provide a clarification within the inclusion criteria.

Description of Change	Rationale	Section Changed
The phrase "augmented rental clearance" was corrected to say "allergic rhinoconjunctivitis."	Correction of a typo.	Section 7.2.1 Inclusion Criteria, #5
A clarification was made that, for adolescents, a parent or legal guardian must also provide informed consent. Additionally, the row for "informed consent" was modified to say "informed consent/assent" within the schedule of events table.	For clarification.	Section 7.2.1 Inclusion Criteria, #7 Table 3 Schedule of Events

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Locations	Approximately 630 adult and adolescent patients will be enrolled at multiple sites across North America and Europe.
Principal Investigator	To be determined
Objectives	**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. *Note: The combined symptom and medication score (CSMS) is defined as the daily combined allergic rhinitis and conjunctivitis total symptom score (TSS: calculated as the sum of total nasal symptom score [TNSS] and total ocular symptom score [TOSS]) plus daily medication score (DMS).* **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 • To assess the immunogenicity of REGN1908 and REGN1909
Study Design	This is a phase 3, randomized, double-blind, parallel-group, multi-dose study in approximately 630 cat-allergic adult (≥18 years of age) and adolescent patients (ages ≥12 to <18 years), where permitted, with allergic rhinitis with or without conjunctivitis and with or without asthma. • 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 and medication use requirements are met during the baseline period. • Randomization to 1 of 2 treatment arms (1:1) o REGN1908-1909 600 mg (300 mg per monoclonal antibody [mAb]) o Placebo that replaces REGN1908-1909 • Study drug will be administered Q12W for a total of 5 administrations • End of treatment visit at week 60 • End of study safety follow-up visit at week 72 The screening period is set up to be a long enough duration so that the baseline assessment will occur outside of relevant pollen seasons for patients who are pollen allergic. 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.
Study Duration	The duration of the study for a patient is approximately 72 weeks, excluding the screening period of up to 12 weeks.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit or withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

Target Population	Male and female patients 12 years of age and older (≥12 to <18 years of age, where permitted) living with at least 1 cat who have allergic rhinitis with or without conjunctivitis symptoms and with or without asthma with cat sensitization confirmed at screening will be enrolled after they meet a symptom and medication requirement at baseline. Other inclusion and exclusion criteria apply.
Sample Size:	Approximately 630 patients will be enrolled.
Treatment **Study Drug and Placebo Dose/Route/Schedule:**	• REGN1908-1909 600 mg (300 mg per mAb), administered by subcutaneous (SC) injections Q12W for a total of 5 doses • Matching placebo that replaces REGN1908-1909 SC Q12W
Endpoints	**Primary Endpoint** The primary endpoint is the daily CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo. *Note: CSMS is defined as the daily combined allergic rhinitis and conjunctivitis TSS (calculated as the sum of TNSS and TOSS) plus daily medication score (DMS).* **Key Secondary Endpoints** The key secondary endpoints, specified without order, are: • Daily TNSS, averaged over the last 12 weeks of treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from pre-treatment baseline in average CSMS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from pre-treatment baseline in average TNSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Daily TSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from pre-treatment baseline in average TSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from baseline to the end of treatment (week 60) in cat SPT mean wheal diameter in patients who receive REGN1908-1909 versus **Other Secondary Endpoints** Other secondary endpoints, specified without order, are:

- 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
- Percent change from pre-treatment baseline in average CSMS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TNSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Daily TSS score, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TOSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Daily TOSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TOSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from baseline to week 12 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Percent change from baseline to week 60 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Percent change from baseline to week 12 in cat skin prick test (SPT) mean wheal diameter in patients who receive REGN1908-1909 versus placebo
- Change from baseline to week 12 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Change from baseline to week 60 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Change from baseline to week 60 in RQLQ(S)+12 in patients who receive REGN1908-1909 versus placebo
- DMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo

	• DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from pre-treatment baseline in average DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo • Percent change from baseline to end of study (week 72) in cat SPT mean wheal diameter in patients who receive REGN1908-1909 versus placebo • Asthma daily symptom (ADS) score, 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 who receive REGN1908-1909 versus placebo • Asthma daily symptom (ADS) score, 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 who receive REGN1908-1909 versus placebo • Daily TOSS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo • Change from baseline to week 60 in ACQ-5 in patients with asthma who receive REGN1908-1909 versus placebo • Daily number of nighttime awakenings, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma who receive REGN1908-1909 versus placebo • Daily number of nighttime awakenings, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients with asthma who receive REGN1908-1909 versus placebo • Incidence of treatment-emergent adverse events (TEAEs), AESIs, and serious TEAEs throughout the study (weeks 0 to 72) • Total REGN1908 and REGN1909 concentration in serum over the study duration (weeks 0 to 72) • Incidence of treatment-emergent anti-drug antibodies (ADAs) to REGN1908 and REGN1909 throughout the study (weeks 0 to 72)
Procedures and Assessments	Efficacy assessments will include: TNSS, TOSS, TSS (calculated as TNSS+TOSS), DMS, CSMS (calculated as TSS+DMS), ANSD score, ADSD score, nighttime awakenings and asthma rescue medication use, ACQ-5, RQLQ(S), Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), spirometry, SPT with cat allergen and other relevant allergen extracts, and serum for sIgE for cat and other allergens.

	Patients will be asked throughout the study about their continued exposure to cat(s). Patients will also be asked questions in the Patient Experience Assessment at week 60 to characterize exposure to their cat(s) in order to further inform interpretation of efficacy results. Safety assessments will include monitoring laboratory tests (hematology, blood chemistry, urinalysis, pregnancy tests), weight, vital signs, physical examination, ECG, adverse events (AEs), and concomitant medications. Samples will be collected for pharmacokinetic (PK), immunogenicity, and exploratory research.
Statistical Plan	**Justification of Sample Size** The sample size will be approximately 315 patients per arm, for a total of 630 patients. This study is powered to detect differences between REGN1908-1909 and placebo on the primary endpoint of daily average CSMS averaged over the last 12 weeks of the treatment period (weeks 48 to 60 primary) 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 average CSMS 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) by the last 12 weeks (weeks 48 to 60), the sample size is 315 patients per arm. A 2-sample t-test with 2-sided alpha of 0.05 was assumed. Calculations were performed using nQuery+nTerim 4.0. A 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 TNSS (SD=2.3 and mean in placebo=3.3) during the primary efficacy period, respectively. Estimates of mean in the placebo and common variability 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. **Primary Efficacy Analysis** The primary analysis of the efficacy endpoint, the daily CSMS averaged over the last 12 weeks of the treatment period (weeks 48 to 60), will be analyzed on the full analysis set (FAS), which consists of all randomized patients. 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, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed effects and the baseline CSMS as a covariate. The average CSMS (max score 38/day) will be calculated based on the sum of daily TNSS (max score 12/day), daily TOSS (max score 6/day), and daily medication scores (DMS, max of 20/day) recorded over the duration of the

last 12 weeks. Only days with observed data will be included in the calculation of average score. Additional details are provided in Table 5 within the protocol body.

The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the primary endpoint are summarized in the Primary Efficacy Analysis section of the Statistical Methods section within the protocol body.

Secondary Efficacy Analyses

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

The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the secondary endpoint is similar to the primary endpoint, summarized in the Secondary Efficacy Analysis section of the Statistical Methods section within the protocol body.

Control of Multiplicity

Multiplicity is considered for testing multiple endpoints. The overall type-I error rate will be controlled at the 2-sided 0.05 level.

A non-binding futility interim analysis (IA) is planned in this study 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.

At the final analysis, hierarchical testing procedure is proposed to strongly control the family wise type-I error rate for testing the primary and key secondary endpoints. Two-sided alpha of 0.049 will be allocated to the endpoints relating to the 12 weeks of the treatment period. The detailed hierarchical order will be specified in the study SAP.

1. INTRODUCTION

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 (Heinzerling, 2009). Approximately 12% to 15% of the United States (US) population has a known sensitivity to cat allergen (Salo, 2011). About 25% to 34% of households in Europe and the US reported owning a cat in the home (Humane Society of United States, 2021) (The European Pet Food Industry, 2019).

Felis domesticus allergen 1 (Fel d 1) is produced by the skin and by salivary and lacrimal glands of the cat (Kleine-Tebbe, 1993) (Grönlund, 2009). 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 (van Ree, 1999). 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 (Bollinger, 1996) (Bollinger, 1998) (Niesler, 2016), 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 (Karlsson, 2004). Additionally, cat allergen is also challenging to remove since it is buoyant and tends to be "sticky" and can remain in homes for months after cat removal (Bateman, 1999) (Chapman, 2001) (Wood, 1989). Therefore, it is difficult to avoid exposure to cat allergen in the environment.

Nasal and eye symptoms are the most frequently reported and most bothersome of all cat allergy symptoms. While treatment of cat allergy includes a recommendation for removal of the cat from the home, often patients or families will refuse to remove the cat from the home due to emotional attachment. As such, despite recommendations, patients continue to live with their cat(s) (Coren, 1997). Rhinoconjunctivitis is treated with antihistamines and intranasal corticosteroids (INCS), which are only moderately effective for nasal symptoms (Ciprandi, 2011). The best reported treatment effects for antihistamines and INCS are 5% to 11% relative reduction of total nasal symptoms compared to placebo (Durham, 2016). Allergic conjunctivitis symptoms are typically treated with topical antihistamines that are sometimes combined with mast cell stabilizers (Mounsey, 2016). Although nasal symptoms are often considered most bothersome, eye symptoms commonly occur with rhinitis. Epidemiologically, it is challenging to define an exact prevalence of eye symptoms (Bousquet, 2001). However, available reports indicate that the majority of allergic rhinitis patients do experience ocular symptoms that result in significant impact on quality of life (Bielory, 2007) (Gomes, 2014) (Riedi, 2010).

The association between cat allergy and asthma is significant. Approximately 30% of allergic asthmatics reportedly have a concomitant allergy to cats (Arbes, 2007). 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 (Giavina-Bianchi, 2016). Patients with high concentrations of cat allergen-specific IgE are at higher risk for oculo-nasal and/or asthma symptoms, or both (Olivieri, 2016) (Perzanowski, 2016).

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 (Walker, 2011) (Zuberbier, 2010). 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 (James, 2011) (Kündig, 2010). Clinical symptom improvement correlates with the ability of blocking IgG4s to compete with IgE for allergen binding. 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 (Durham, 2012) (Leung, 2010) (Scadding, 2017).

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 (van Ree, 1999) and accounts for 60% to 90% of the total allergenic activity in cat dander (Kleine-Tebbe, 1993).

These human high-affinity IgG4 mAbs targeted to the major cat allergen are designed to block Fel d 1 from binding to IgE, as well as or better than those naturally produced during SIT (Orengo, 2018).

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(0–1 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). All patients included in the study demonstrated an EAR within 2 hours of the Controlled Cat Allergen Challenge at screening. EAR was defined as a reduction in FEV1 by ≥20% upon exposure to controlled cat allergen in an EEU. A single dose of REGN1908-1909 provided a rapid and durable reduction in cat allergen induced acute bronchoconstriction, as shown by the increased time to EAR in cat-allergic, mild asthmatic patients upon EEU exposure to cat allergen at 8 days (earliest time evaluated) and up to day 85 (latest time 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 with placebo, REGN1908-1909 significantly prevented cat allergen induced declines in FEV1 over 0 to 2 hours during the Controlled Cat Allergen Challenge in the EEU up to 85 days after a single dose. The difference from placebo was 13.6% at day 8 and was consistent through day 85. 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.

Targeted, passive immunotherapy of cat allergy with REGN1908-1909 may provide rapid systemic relief of the constellation of "unified airway" respiratory (upper and lower) and ocular symptoms. As compared to SIT, REGN1908-1909 may potentially: 1) be safer as the allergic patient is not exposed to actual allergen, 2) offer more convenience, as a single SC dose may prevent allergic symptoms for months, 3) broaden the pool of patients to derive benefit including asthmatics who may have previously been contraindicated for SIT, and 4) have a faster onset of action, as demonstrated in the study R1908-1909-ALG-1325, which achieved clinical efficacy 8 days after a single dose of 600 mg/kg, the earliest time point at which efficacy was assessed. Furthermore, in study R1908-1908-ALG-1703, REGN1908-1909 was able to increase the median time to early asthma reaction (EAR) in an EEU by day 8. The effect persisted through day 85 (the last time point evaluated). Additionally, REGN1908-1909 significantly prevented cat allergen induced reductions in FEV1 during the EEU sessions. The amount of allergen tolerated was 3 times higher in the active group compared to the placebo group.

This phase 3 study (R1908-1909-ALG-2102) aims to investigate the effect of REGN1908-1909 on the treatment of cat allergic patients with allergic rhinitis with or without conjunctivitis and with or without asthma. Additionally, given that it is expected that at least 30% of the population enrolled will have concomitant asthma, the effect on asthma symptoms, asthma rescue medication use, lung function, and overall asthma control will be evaluated.

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

2. STUDY OBJECTIVES

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.

Note: The combined symptom and medication score (CSMS) is defined as the daily combined allergic rhinitis and conjunctivitis total symptom score (TSS: calculated as the sum of total nasal symptom score [TNSS] and total ocular symptom score [TOSS]) plus daily medication score (DMS).

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
- To assess the immunogenicity of REGN1908 and REGN1909

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.

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

A cocktail of 2 anti-Fel d 1 (mAbs) (REGN1908-1909) is more effective at reducing allergic rhinitis and conjunctivitis symptoms and medication scores when compared to placebo during weeks 48 to 60 of the treatment period.

Treatment Q12W will result in a durable treatment effect that persists through the approximate 1-year treatment period.

Refer to Section 11.1 for the statistical hypothesis.

3.2. Rationale

3.2.1. Rationale for Study Design

REGN1908-1909, fully human IgG4 anti Fel d 1 mAbs, bind specifically, non-competitively, and with high affinity to different epitopes on Fel d 1, the major cat allergen. By the mAbs attaching to this relevant allergen, there will be interference of Fel d 1 binding to and crosslinking IgE, resulting in a blockade of the subsequent allergic cascade in cat allergic subjects when exposed to cat allergen. The purpose of this study is to demonstrate that REGN1908-1909 reduces the symptoms associated with cat allergy. The focus of the trial will be on allergic rhinitis and conjunctivitis symptoms. Efficacy will be evaluated by assessing the reduction of allergic nasal and ocular symptoms, and the reduction in the use of allergy rescue medications in patients exposed to cat in their home. However, given that more than 50% of cat-allergic patients can have a diagnosis of co-morbid asthma (Giavina-Bianchi, 2016), an evaluation of the effect on asthma will also be conducted.

Patients with cat allergy who are ≥12 to <18 years of age, where permitted based on local regulations, and older (≥18 years of age) will be considered for this trial. Allergic rhinitis is a common condition in adolescents, with ~80% of patients developing allergic rhinitis symptoms before age 20 years (Gentile, 2013). The pathophysiology, diagnosis and treatment of allergic rhinitis in adolescents is thought to be similar to adults (Izquierdo-Domínguez, 2013) (Dykewicz, 2020). Similar to adults, adolescents experience symptoms of allergic rhinoconjunctivitis and related impact on quality of life (Blaiss, 2018). In addition, the diagnostic considerations and treatment recommendations do not differ between adolescents and adults with allergic rhinitis and/or asthma (Dykewicz, 2020) (Krishnan, 2021). The cumulative pharmacokinetic (PK) data from the 3 completed clinical studies were assessed to support the inclusion of adolescents in this phase 3 field study. The PK of REGN1908 and REGN1909 has been consistent across all clinical trials, exhibiting linear, dose proportional PK. Given that REGN1908 and REGN1909 are monoclonal antibodies mAbs directed at an exogenous target, administration of REGN1908 and REGN1909 is not expected to affect endogenous pathways, and physiological differences between adolescent and adult populations would not affect target availability or engagement. As is typical for a monoclonal antibody, exposure to REGN1908 and REGN1909 is inversely proportional to body weight, as body weight is often the most influential covariate affecting PK of mAbs (Temrikar, 2020) (Shi, 2010) (Xu, 2020). However, the exposure difference by body weight does not appear to translate into meaningful differences in efficacy or safety at the proposed dose, which has generally been well tolerated. The lower end of the proposed

body weight range (≥40 kg) falls within the range of expected body weights for the majority of adolescent subjects and given the overlapping body weight ranges in adults and adolescents, a 600 mg SC dose is expected to yield comparable exposures to REGN1908 and REGN1909 in adolescent populations to those observed in adults. A body weight criterion of ≥40 kg was included in the phase 3 protocol to ensure drug exposure will be in a range that has been previously measured in humans; therefore, only those adolescent patients who fall within the weight parameters already tested in the adult population (≥40 kg) will be included in this study.

The study consists of up to a 12-week screening period. A baseline 15-day assessment of symptoms and medication use is required to ensure that patients are significantly symptomatic despite use of standard of care anti-allergy rescue medications (provided as part of the study). Importantly, the baseline symptom/ medication assessment and 12-week efficacy assessments should occur outside of the relevant pollen season in patients with concomitant seasonal allergies. The extended screening period will allow for these procedures and assessments to occur at temporally appropriate times.

After meeting all inclusion and no exclusion criteria, patients will be randomized to receive REGN1908-1909 or placebo administered SC Q12W. Efficacy will be evaluated over a 12-week period following the initial dosing of REGN1908-1909 or placebo and following the final dose of REGN1908-1909. Twelve-week periods represent a significant time period of a year to measure effectiveness of study drug. The second 12-week period following the last dose of medication, considered the primary efficacy endpoint assessment for this study, will provide evidence of durability of effect for this medication which is intended for chronic use. Due to the various pollens that are prevalent during the spring through the autumn seasons, efficacy assessment will occur over the winter months for those patients with relevant pollen allergies to reduce potential confounding factors that may impact nasal and ocular symptoms.

During the initial 12-week period following the first treatment dose with either REGN1908-1909 or placebo, daily symptoms of allergic rhinitis and conjunctivitis will be captured as well as the use of study provided allergy rescue medication for the treatment of allergic rhinitis and conjunctivitis. In patients with co-morbid asthma, the asthma daytime and nighttime symptom questionnaires, nighttime awakening, asthma rescue medication use, spirometry, and the Asthma Control Questionnaire 5 Question Version (ACQ-5) will also be collected.

Following the initial 12-week assessment period, all patients will continue to receive REGN1908-1909 or placebo Q12W with the last dose administered at approximately week 48. Following the last dose, daily symptoms of allergic rhinitis and conjunctivitis will be captured as well as the use of study provided allergy-relieving rescue medication for the treatment of allergic rhinitis and conjunctivitis for an additional 12 weeks (weeks 48 to 60). In patients with asthma, the ACQ-5, spirometry, ANSD and nighttime awakenings, and ADSD and asthma rescue medication usage will be collected. The assessments collected during the last 12 weeks of the treatment period will be utilized to demonstrate durability of the treatment effect.

Evaluations of efficacy will occur during pre-specified 12-week periods (weeks 0 to 12 and weeks 48 to 60). Given that the majority of patients are expected to have sensitizations to allergens other than cat, the efficacy assessment periods will be planned to occur at times of year when there will be limited interference by other allergens for those patients with other co-morbid clinically relevant allergies.

3.2.2. Rationale for Dose Selection

Preclinical:

Blocking potency of the cocktail of anti-Fel d 1 mAbs was characterized in a preclinical basophil activity test using fresh basophils from cat allergic patients. The utilization of both antibodies (REGN1908-1909) was more effective than either REGN1908 or REGN1909 alone, in the majority of patients in blocking Fel d 1 binding to polyclonal human IgE and inhibiting activation of basophils, as measured by flow cytometry by percent inhibition of phosphorylated extracellular signal-regulated kinase (pERK) responses, from cat allergic patients.

Clinical:

The PK of REGN1908 and REGN1909 has been consistent across all clinical trials, exhibiting linear PK and a terminal half-life of approximately 31.0±5.9 days and 22.4±3.8 days for REGN1908 and REGN1909, respectively. In a phase 1b study (R1908-1909-ALG-1325) designed to reduce nasal symptoms after a nasal allergen challenge and a phase 2 study (R1908-1909-ALG-1703) that evaluated efficacy of preventing asthma in an EEU, a dose of 600 mg (300 mg/mAb) was well tolerated and maintained efficacy for up to 12 weeks, suggesting that this dose will be safe and efficacious in a phase 3 field study, including after repeat administration. PK data from previous clinical trials in cat allergic humans were used to estimate PK parameters and then simulate repeat SC doses for 300 mg/mAb every 3 months. Maximum (C_{max}) and trough (C_{trough}) total antibody concentrations in serum are within approximately 10% of single dose C_{max} and C_{trough} values, indicating that accumulation is expected to be minimal, while also maintaining a C_{trough} concentration that is associated with efficacy.

3.3. Risk-Benefit

REGN1908 and REGN1909 are human mAbs of the IgG4 isotype that bind different epitopes on Fel d 1 simultaneously, non-competitively, and with high affinity. REGN1908 and REGN1909 are being developed as an antibody cocktail (designated as REGN1908-1909). REGN1908-1909 blocks Fel d 1 from binding and crosslinking receptor bound IgE on the surface of allergic effector cells, thus preventing initiation of the cat allergic response. The clinical proof-of-mechanism study (R1908-1909-ALG-1325) examined the potential of REGN1908-1909 to block acute allergic symptoms triggered by nasal provocation with cat extract in cat allergic patients. The majority of patients receiving REGN1908-1909 experienced symptom amelioration, with at least 50% of patients achieving 60% improvement in TNSS at every time point assessed during nasal allergen challenges up to 12 weeks post-treatment (day 85, last time point assessed) with efficacy demonstrated as early as the first time point evaluated (day 8). This suggests that a majority of cat allergic patients who were treated with REGN1908-1909 may derive benefit by experiencing reduced rhinitis symptoms upon challenge with cat allergen. Additionally, in a proof-of-concept study (R1908-1909-ALG-1703) in cat allergic patients with GINA 1 asthma, REGN1908-1909 increased the time to EAR in the majority of patients and increased the cumulative cat allergen tolerated during cat allergen EEU challenge by 3 fold. These effects were first noted on day 8 (initial time point evaluated post study drug administration) and persisted up to 12 weeks post-treatment, suggesting a potential benefit in cat allergic individuals with mild asthma. Taken together, these results support that a single dose of the REGN1908-1909 cocktail demonstrated a rapid and clinically meaningful effect in reducing the allergic airway response in cat allergic

patients. The treatment may offer a rapid and potentially effective approach for the treatment of cat allergy in patients where there is ongoing exposure to cat allergen or cats cannot be avoided.

REGN1908-1909 has been used to treat 83 subjects in 3 completed clinical studies with no significant clinical safety findings observed to date, including no deaths, and no cases of systemic hypersensitivity, or anaphylaxis. No important identified risks have been established. The important potential risks with REGN1908-1909 (based on preclinical evaluation, mechanism of action targeting an exogeneous antigen, and risks associated with mAbs in general) include systemic hypersensitivity reactions and immunogenicity. REGN1908-1909 has been generally well tolerated and risks have been adequately managed.

To date, no significant safety information with regard to the important potential risks of systemic hypersensitivity reactions and immunogenicity has been reported. Currently, the available safety data along with the risk minimization and monitoring activities support the continued development of REGN1908-1909.

As with most other protein therapeutics that are administered SC, injection site reactions may occur and may be treated symptomatically. Among the 3 completed studies, injection site reactions were reported in 6 patients that received REGN1908-1909, compared to 2 patients in the placebo groups, and all were mild in severity. Allergy/hypersensitivity reactions may develop; the most concerning are those that may develop immediately or within a few hours of administration of REGN1908-1909. Because REGN1908-1909 is composed of antibodies whose sequence is fully human, the risk of these immediate reactions is considered to be extremely low. Emergency equipment and medication for the treatment of these potential adverse effects (including but not limited to antihistamines, corticosteroids, acetaminophen, and/or epinephrine) are available for immediate use in this study. Considering the safety data and the exogenous nature of the target antigen, the risk of other adverse reactions is considered to be low. A risk-benefit statement with respect to the overall development program is provided in the Investigator's Brochure.

An Independent Data Monitoring Committee (IDMC) will be involved in the review of unblinded data in an ongoing manner (refer to Section 6.3.1).

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees (ECs) to enable initiation of study sites for this study, as allowed by local laws and regulations.

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is the daily CSMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo.

Note: CSMS is defined as the daily combined allergic rhinitis and conjunctivitis TSS (calculated as the sum of TNSS and TOSS) plus daily medication score (DMS).

4.2. Secondary Endpoints

The key secondary endpoints, specified without order, are:

- Daily TNSS, averaged over the last 12 weeks of treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average CSMS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TNSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Daily TSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from baseline to the end of treatment (week 60) in cat SPT mean wheal diameter in patients who receive REGN1908-1909 versus

Other secondary endpoints, specified without order, are:

- 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
- Percent change from pre-treatment baseline in average CSMS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TNSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo

- Daily TSS score, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TOSS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Daily TOSS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average TOSS, over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo.
- Percent change from baseline to week 12 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Percent change from baseline to week 60 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Percent change from baseline to week 12 in cat skin prick test (SPT) mean wheal diameter in patients who receive REGN1908-1909 versus placebo
- Change from baseline to week 12 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Change from baseline to week 60 in FEV1 in patients with asthma who receive REGN1908-1909 versus placebo
- Change from baseline to week 60 in RQLQ(S)+12 in patients who receive REGN1908-1909 versus placebo
- DMS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average DMS, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients who receive REGN1908-1909 versus placebo
- Percent change from baseline to end of study (week 72) in cat SPT mean wheal diameter in patients who receive REGN1908-1909 versus placebo
- Asthma daily symptom (ADS) score, 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 who receive REGN1908-1909 versus placebo
- Asthma daily symptom (ADS) score, 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 who receive REGN1908-1909 versus placebo

- Daily TOSS, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Change from baseline to week 60 in ACQ-5 in patients with asthma who receive REGN1908-1909 versus placebo
- Daily number of nighttime awakenings, averaged over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma who receive REGN1908-1909 versus placebo
- Daily number of nighttime awakenings, averaged over the last 12 weeks of the treatment period (weeks 48 to 60), in patients with asthma who receive REGN1908-1909 versus placebo
- Incidence of treatment-emergent adverse events (TEAEs), AESIs, and serious TEAEs throughout the study (weeks 0 to 72)
- Total REGN1908 and REGN1909 concentration in serum over the study duration (weeks 0 to 72)
- Incidence of treatment-emergent anti-drug antibodies (ADAs) to REGN1908 and REGN1909 throughout the study (weeks 0 to 72)

4.3. Exploratory Endpoints

The exploratory endpoints are:

- The number of "well days" in those who received REGN1908-1909 versus placebo, 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" in those who received REGN1908-1909 versus placebo, 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 ADS score, over the initial 12 weeks of the treatment period (weeks 0 to 12), using ADSD and the ANSD in patients with asthma who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average frequency of asthma rescue medication use, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients with asthma who receive REGN1908-1909 versus placebo
- 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 who receive REGN1908-1909 versus placebo
- Percent change from pre-treatment baseline in average DMS, over the initial 12 weeks of the treatment period (weeks 0 to 12), in patients who receive REGN1908-1909 versus placebo
- Change from baseline to week 12 in RQLQ(S)+12 in patients who receive REGN1908-1909 versus placebo

- Change from baseline to week 12 in Asthma Control Questionnaire 5 Question Version (ACQ-5) in patients with asthma who receive REGN1908-1909 versus placebo
- 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 who receive REGN1908-1909 versus placebo
- 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 who receive REGN1908-1909 versus placebo

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), medical history (including allergy history), medication history, asthma history, SPT mean wheal diameter for cat and other allergens, and cat and Fel d 1 sIgE levels for each patient.

5.2. Efficacy Variables

Efficacy variables include TNSS, TOSS, TSS (which results from adding the TNSS and TOSS), DMS, CSMS (which results from adding the DMS and TSS), mean wheal diameter of cat SPT, and RQLQ(S) and spirometry (in all patients at screening and randomization, and only in patients with asthma after randomization). For patients with asthma, ACQ-5, asthma symptoms, and rescue medication use for asthma will also be evaluated.

5.3. Safety Variables

Safety variables include AEs, vital signs, physical examinations, electrocardiogram (ECG), and laboratory safety tests.

5.4. Pharmacokinetic Variables

The pharmacokinetic variables are total concentration of REGN1908 and total concentration of REGN1909 in serum at each time point. Samples in this study will be collected using a sparse sampling schedule, eg, only 1 blood sample for drug concentration measurement is collected at any single clinic visit. These sampling time points are specified in Table 3.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 3.

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables include, but are not limited to serum sIgE for cat and Fel d 1, serum sIgE for other relevant allergens (such as but not limited to Fel d 2, 4, and 7), SPT results for cat, and other relevant allergens.

Exploratory aims of biomarkers analyses include, but are not limited to:

- To identify genomic associations with clinical or biomarker response to treatment with REGN1908-1909
- To identify genomic variants associated with the prognosis or progression of cat allergy, asthma and related diseases

These results may be reported outside of the clinical study report (CSR).

6. STUDY DESIGN

6.1. Study Description and Duration

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.

- 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 (300 mg per mAb)
  - Placebo that replaces REGN1908-1909
- Study drug will be administered Q12W for a total of 5 administrations
- End of treatment visit at week 60
- End of study safety follow-up visit at week 72

The screening period is set up to be a long enough duration so that the baseline assessment will occur outside of relevant pollen seasons for patients who are pollen allergic. 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. The study flow diagram is depicted in Figure 1. For prohibited medications and washout durations for different study procedures and assessment periods, see Section 8.9.1.

Screening:

During screening at 1 or more visits, patients undergo assessments of eligibility, including skin testing to cat allergen as well as serum specific IgE assessment to cat and Fel d 1. In-clinic spirometry will also be completed during screening. Provided that the initial eligibility criteria at screening are met, patients will be given an electronic diary to capture their allergic rhinitis and conjunctivitis symptoms as well as anti-allergy rescue medication use to capture symptoms and medication use for a 15-day baseline assessment (outside of any relevant pollen seasons for individuals with other seasonal allergies), which occurs as part of the screening period. Asthma daytime and nighttime symptom diaries, nighttime awakenings, and asthma rescue medication use will also be collected in patients with asthma during the baseline assessment.

Rescreening is allowed up to 1 time. Patients cannot be rescreened based on skin testing or sIgE to cat not meeting eligibility. Baseline period assessment for symptom and medication requirements may not be repeated if patients do not meet eligibility criteria.

Baseline Period within Screening:

The baseline assessment period is up to 21 days, and should be completed for a minimum of 15 consecutive days during the approximately 12-week screening period. This period is utilized to demonstrate that patients are sufficiently symptomatic due to cat exposure while taking standard of care anti-allergy rescue medications provided during the study (oral antihistamine, antihistamine eye drops, intranasal corticosteroid; Section 8.2). Patients will complete an e-diary to record their nasal, ocular, and asthma symptoms as well as anti-allergy rescue medication use up to a 3-week period during screening (the 3-week period allows for up to 6 days of training or troubleshooting, if required). Patients will be required to have experienced allergic rhinoconjunctivitis symptoms, as measured by the TSS, and to have used anti-allergy rescue medications, as specified, for at least 8 days of a consecutive 15-day period during this time. Patients must meet a daily total rhinitis and conjunctivitis symptom threshold of at least 8 of 18 on at least 8 days of the consecutive 15-day baseline assessment period and use standard therapeutic doses of the anti-allergy rescue medications on 8 of the consecutive 15 days during the baseline assessment period. Adequate standard of care treatment is defined as currently approved doses of antihistamines and intranasal corticosteroids provided during the study.

The baseline assessment will occur outside of relevant pollen season for those patients with seasonal allergies.

Patients will complete baseline Patient Global Impression of Severity (PGIS) and RQLQ(S) during the baseline assessment period. Additionally, patients with asthma will complete the Asthma daytime and nighttime symptom diaries (ADSD and ANSD), ACQ-5, nighttime awakenings, and asthma rescue medication use during the baseline assessment period.

If missing data are reported due to documented e-diary malfunction (eg, technical issues that are reported to the vendor), then the baseline assessment period may be extended accordingly, allowing the 15-day period to be re-started, to ensure that a consecutive 15 day period can be obtained. In such a circumstance, the medical monitor should be consulted, and agreement must be obtained with the sponsor.

Treatment Period:

Patients meeting eligibility criteria and symptom threshold will be randomized to either REGN1908-1909 or placebo. Patients will be administered either REGN1908-1909 or placebo for a total of 5 study drug administrations which will be given Q12W. The initial 12 weeks (weeks 0 to 12) and the last 12 weeks (weeks 48 to 60) following the first dose of study drug will be the efficacy assessment periods. The primary efficacy assessment period is the last 12 weeks of the treatment period (after the fifth administration of study drug).

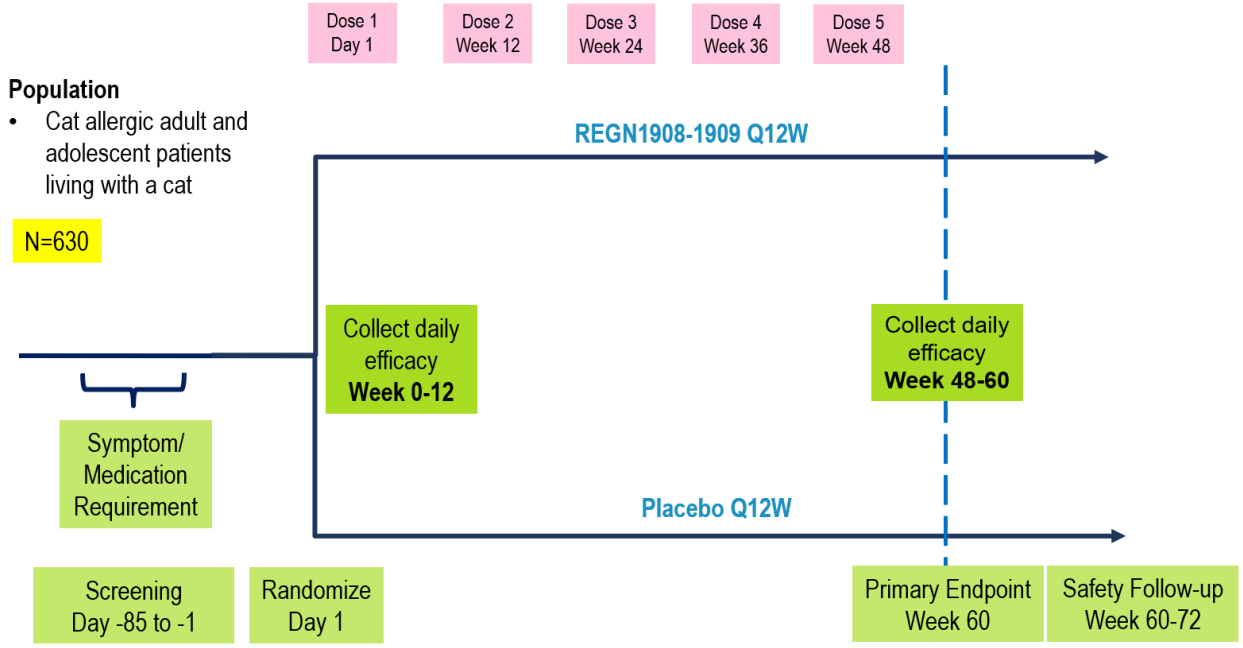
The allergic rhinitis symptoms are measured by the total nasal symptom score (TNSS), based on nasal congestion, sneezing, runny nose, and itching of the nose; each symptom is graded 0 (none), 1 (mild), 2 (moderate), and 3 (severe) for a maximum score of 12. Allergic conjunctivitis is measured by the TOSS, based on itching/redness/gritty feeling and tearing/watering; each of the 2 symptoms is graded 0 (none), 1 (mild), 2 (moderate), and 3 (severe) for a maximum score of 6. A TSS results from adding the TNSS and TOSS, yielding a minimum score of 0 and a maximum score of 18. The allergic nasal and ocular symptoms will be recorded daily by the patients using the e-diary.

Patients will be provided with open-label allergy-relieving rescue medications (oral antihistamine, antihistamine eye drops, intranasal corticosteroid; Section 8.2) starting at the baseline assessment period (during screening), visit 3 (day 1), and during the study, which they may take as needed in standard therapeutic doses during the study to treat their allergic rhinitis/conjunctivitis symptoms. Patients will be asked to record their daily anti-allergy rescue medication use using an e-diary, including the specific medication name and dose. This information will be used to calculate the DMS 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).

The CSMS (combined symptom and medication score) is calculated by adding the TSS (TNSS+TOSS) and DMS together, with scores ranging between 0 and 38. RQLQ(S) will also be collected at baseline and during the initial 12-week efficacy assessment period as well as during the last 12 weeks of the treatment period.

During the efficacy assessment periods, from the first day of dosing through the initial 12 weeks of the study and during the final efficacy assessment period (weeks 48 to 60), patients with comorbid asthma will complete the Asthma Daytime Symptom Diary (ADSD) and questions on asthma rescue medication use; this will occur each evening. Every morning, patients with co-morbid asthma will complete the Asthma Nighttime Symptom Diary (ANSD), and questions on nighttime awakening. In-clinic spirometry and ACQ-5 will be collected in patients with co-morbid asthma to compare any changes between baseline and the end of the initial 12-week efficacy assessment and the last 12 weeks of the treatment period.

Figure 1: Study Flow Diagram



6.1.1. Study Stopping Rules

6.1.1.1. Study Stopping Criteria

There are no pre-specified stopping rules; however, appropriate action, if needed, will be taken based upon data review and in consultation with an IDMC (described in Section 6.3). Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

6.1.2. End of Study Definition

The end of study is defined as the date the last patient completes the last study visit or withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned 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 the IDMC charter and SAP.

Unblinded results can only be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study, if the non-binding futility criterion is met. A detailed plan will be defined in the IDMC charter and SAP, including plans to describe the processes intended to control access to comparative interim results to preserve trial integrity. Individuals involved in the conduct of the study (ie, patients, Investigators, Study Team, and Project Team, etc.) will have no access to the IA results.

For the IA, the efficacy endpoints will be analyzed using the same methods described in the efficacy analyses section (Section 11.4.3.1). The analysis population for the interim futility analysis will include at least the first 40% of the randomized patients. The analysis of the endpoints will use all the data collected for the analysis population up to the IA cutoff time. An administrative penalty of 0.001 will be taken from the significance level used at final analysis (ie, 2-sided 0.049 will be used for the final analysis).

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor patient safety and efficacy data. The IDMC is composed of members who are independent from the sponsor and the study investigators. The IDMC will provide oversight of patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment. As described in Section 6.2, an IA will be performed by independent statisticians that support the IDMC. The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in these studies. All activities and responsibilities of the IDMC are described in the IDMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 630 adult and adolescent patients will be enrolled at multiple sites across North America and in Europe.

7.2. Study Population

Male and female patients ≥12 to <18 years of age, where permitted, and older (≥18 years of age) living with at least 1 cat who have allergic rhinitis with or without conjunctivitis symptoms and with or without asthma with cat sensitization confirmed at screening will be enrolled after they meet a symptom and medication requirement at baseline.

7.2.1. Inclusion Criteria

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

1. Generally healthy males and females who are 12 years and older at the time of screening.
    - Note that for those countries where local regulations or approvals permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age.
2. Weight must be ≥40 kg at the time of screening
3. Documented or patient reported history (for at least 2 years) of symptomatic cat allergen-triggered allergic rhinitis with or without conjunctivitis and with or without asthma as defined by all of the following criteria:
    a. Positive skin prick test (SPT) with cat hair extract (mean wheal diameter at least 5 mm greater than a negative control) at screening
    b. Positive allergen-specific IgE (sIgE) tests for cat and Fel d 1 (both ≥0.7 kUa/L at screening)
    c. Documented or patient reported history of nasal and/or ocular symptoms upon cat exposure
    d. Symptomatic despite the use of medications to treat their nasal and/or ocular symptoms
4. At least 1 generally healthy cat (that is unlikely to die during the study) living in the home resulting in regular exposure
5. A daily total rhinitis/conjunctivitis symptom score (total symptom score [TSS]) of at least 8 of 18 during at least 8 days of the 15-day baseline assessment period and use of standard, therapeutic doses of pharmacotherapy for the treatment of allergic rhinoconjunctivitis on at least 8 days of the 15-day baseline assessment period.
6. Willing and able to comply with clinic visits and study-related procedures.
7. Provide informed consent signed by study patient or legally acceptable representative. For adolescents, a parent or legal guardian must provide signed informed consent (patients must also provide separate informed assent to enroll in the study, and the assent

documented either in a separate informed assent form [IAF] or in the informed consent form [ICF] signed by the parent(s)/legal guardian [as appropriate based on local regulations and requirements]).

8. Able to understand and complete study-related questionnaires.

7.2.2. Exclusion Criteria

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

1. History of significant multiple and/or severe allergies, as assessed by the investigator, that would potentially interfere with the assessments during the baseline and 12-week efficacy assessment periods or confound results, per investigator discretion, including significant rhinitis or sinusitis due to daily contact with other allergens causing symptoms that are expected to coincide with the baseline period or any of the efficacy assessment periods
2. Received REGN1908-1909 in a prior REGN1908-1909 clinical trial (receipt of placebo in a previous trial is allowed)
3. Active lung disease other than asthma
4. FEV1 less than 70% of predicted at screening or randomization
5. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to screening
6. Persistent chronic or recurring acute infection requiring treatment with antibiotics, antivirals, or antifungals, or any untreated respiratory infections within 4 weeks prior to screening. Patients may be re-evaluated after resolution of symptoms and specified time duration
7. Any laboratory findings showing evidence of organ dysfunction or any clinically significant deviation from the normal range, as decided by the Investigator at the screening visit, including but not limited to
    a. Clinically significant/ active hepatobiliary disease
    b. Abnormal laboratory values at screening, such as
        - Platelets $<100 \times 10^3/\mu L$
        - Neutrophils $<1.5 \times 10^3/\mu L$
        - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2

    NOTE: If an abnormal value is detected at screening, a repeat test can be performed to confirm the abnormality to categorize the patient as a screen failure.
8. Any medical illness, which in the judgment of the investigator could preclude participation in the study or in whom treatment with epinephrine or beta-2 agonists or systemic corticosteroids would pose an increased risk (eg, history of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disease, etc)
9. Patients taking any prohibited treatment (see Section 8.9.1)

10. Use of systemic corticosteroids within 30 days prior to screening visit 1, if used for the treatment of asthma symptoms. Patients may be re-evaluated after resolution of symptoms and specified time duration
11. Use of anti-IgE or other biological therapy (including but not limited to anti IL-5, anti IL-4) that interferes with type 2 disease within 6 months prior to screening visit 1
12. Specific immunotherapy (SIT) with cat allergen or cat vaccine within 6 months prior to screening visit 1. Patients with symptomatic cat allergy despite previous history of SIT (more than 6 months prior to screening visit 1) with cat allergen or vaccine may enroll if SIT was assessed as ineffective, per principal investigator discretion
13. SIT with any allergen other than cat at screening visit 1. Patients who plan to initiate SIT during the trial period will be excluded.
14. Patients who have recently started (within 12 weeks prior to screening visit 1) and plan to continue or plan to start their cat(s) on an anti-allergen cat food (eg, Purina Pro Plan® LiveClear) or other anti-allergen treatment during the study
15. Patients who anticipate major changes in allergen exposure in their home or work environments during baseline and efficacy assessment periods, as assessed by the investigator
16. History of life-threatening asthma, defined as an asthma episode that required intubation, and/or was associated with hypercapnia, respiratory arrest, and/or hypoxic seizures
17. History of intensive care hospitalization for asthma within past 2 years
18. History of intolerance to systemic or topical corticosteroids or antihistamines, or drug treatment excipient
19. History of hypersensitivity to drug treatment excipient or allergies that could represent a substantial risk to the patient in the opinion of the investigator
20. History of nasal polyps
21. History of drug or alcohol abuse within a year prior to screening
22. Any malignancy within the past 5 years, except for basal cell or squamous epithelial cell carcinomas of the skin or carcinoma in situ of the cervix or anus that have been resected, with no evidence of local recurrence or metastatic disease for 3 years
23. Positive serum human chorionic gonadotropin pregnancy test at the screening visit or randomization visit for women of childbearing potential (WOCBP)

    NOTE: Pregnancy testing and contraception are not required for women with documented hysterectomy, bilateral oophorectomy, or tubal ligation
24. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
25. Pregnant or breastfeeding women
26. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study,

and for at least 24 weeks after the last dose. Highly effective contraceptive measures include:

a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
c. bilateral tubal ligation;
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
e. sexual abstinence†, ‡

* WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation

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

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

27. Is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

7.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

REGN1908 and REGN1909 are each formulated in a buffered, aqueous solution at pH 5.8. REGN1908 and REGN1909 drug product will be supplied separately as lyophilized cakes in 20 mL glass vials.

REGN1908 and REGN1909 are provided individually in open-label vials in cartons. A medication numbering system will be used to label unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging; these lists will not be accessible to individuals involved in study conduct. The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the patient. Study drug will be stored at the site at a temperature of 2ºC to 8ºC. Storage instructions will be provided in the pharmacy manual.

For SC administration, these drug products are each reconstituted with 2.3 mL of sterile water for injection, yielding a final concentration of 100 mg/mL REGN1908 or 100 mg/mL REGN1909 in histidine, polysorbate 80, and sucrose. A total volume of 2.0 mL of the reconstituted liquid can be withdrawn from the glass vial. The reconstituted liquids will be mixed as a 1:1 cocktail. The resulting mixture will have a concentration of 100 mg/mL total of REGN1908-1909 (50 mg/mL REGN1908 and 50 mg/mL REGN1909). A 2.0 mL injection of the cocktail will provide a total dose of 200 mg REGN1908-1909. Three 2.0 mL SC injections will be administered for 600 mg total (300 mg per mAb). It is recommended that the 3 SC injections be given in separate locations, either the abdomen, thighs, or upper arms. During the treatment period, there will be 5 visits during which study drug will be administered for a total of 15 injections.

This is a multiple dose study. Study drug will be administered at study site Q12W for a total of 5 administrations. Patients will be randomized in a 1:1 ratio to receive 600 mg REGN1908-1909 or matching placebo that replaces REGN1908-1909.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Rescue Treatments

Patients will be provided with the following medications (or an in-class equivalent, agreed upon with the sponsor) to treat allergic symptoms during the study:

- desloratadine 5 mg (second generation antihistamine)
- olopatadine 1 mg/mL (antihistamine eye drop)
- mometasone furoate 50 ug/dose (intranasal steroid)

From the time of baseline assessment period, patients can utilize the study provided allergy rescue medications (desloratadine, olopatadine and mometasone as specified above) to treat their allergic rhinitis and allergic conjunctivitis symptoms. During the baseline assessment and the efficacy assessment periods of the trial (weeks 0 to 12 and 48 to 60), daily use of rescue medications will be documented in the patient diary. At other non-efficacy periods (weeks 12 to 48), the rescue medication use can be documented in the concomitant medications.

Patients will be asked to refrain from taking specific prohibited medications during the study periods or within the specified time periods, preceding screening, baseline symptom and medication assessment, efficacy periods and at specific time points when skin testing or in-clinic spirometry will be conducted to prevent interference with the procedure (see Section 8.9.1).

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- A serious or severe asthma event deemed related to study drug that in the opinion of the PI would result in increased risk to the patient or a ≥50% decline in FEV1 from pre-treatment baseline
- If, in the investigator's opinion or at the specific request of the sponsor, continuation of study drug would be detrimental to the patient's well-being, or there is no longer any potential for benefit, or if continuation would undermine the scientific integrity of the study
- Specific types of liver dysfunction (eg, Hy's law is met (FDA, 2009))
- Patient withdraws consent/ assent
- In the event of an important protocol deviation, at the discretion of the investigator or the sponsor

8.3.2.2. Reasons for Temporary Discontinuation of Study Drug

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

- An asthmatic patient experiencing an asthma exacerbation and/or has a clinically relevant decrease in FEV1 ≥20% below baseline at a visit during which study drug was scheduled to be dosed, per investigator judgement. In this case, the patient may return to the clinic within the dosing visit window to be re-assessed for eligibility to receive study drug.

- Neutrophil count ≤1.0 x 10^3/μL
- Sustained ALT/AST values greater than 3x the ULN plus total bilirubin >2x ULN or isolated AST/ALT >5x ULN
- Hospitalization
- Other intercurrent illness or adverse event or major surgery that could, in the opinion of the investigator, present an unreasonable risk to the patient as a result of his/her continued use of the study drug

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron medical monitor.

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

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following SC injection of study drug should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.4.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.5. Method of Treatment Assignment

Approximately 630 patients will be randomized in a 1:1 ratio to receive either 600 mg (300 mg per mAb) REGN1908-1909 or placebo according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to age (adolescents vs adults), asthma status (yes vs no), and house dust mite (HDM) sensitivity (<0.7 kUa/L versus ≥0.7 kUa/L).

8.6. Blinding

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

Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review.

8.7. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.3.2).

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

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

8.8. Treatment Logistics and Accountability

8.8.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label unblinded open-label investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging; these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the patient.

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

8.8.2. Supply and Disposition of Treatments

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

8.8.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

8.8.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.9. Concomitant Medications

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

8.9.1. Prohibited Medications

Medications prohibited throughout the entire study are presented in Table 1 and medications prohibited for specific study periods are presented in Table 2.

Table 1: 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 (6 months)
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)

Medication Group	Time Prohibited Before Study (Washout)
Systemic calcineurin inhibitors	Prohibited (14 days)

Table 2: 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 (eg, 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 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)

8.9.2. Permitted Medications

Study provided rescue medications (desloratadine, olopatadine, and mometasone furoate, or in-class equivalent) can be used, as needed, throughout the study. The use of medications not listed as prohibited, will be allowed outside of the baseline and efficacy assessment periods (see Section 8.2).Treatment for acute reactions is allowed during the study (see Section 8.2).

If a patient intends to receive a COVID-19 vaccine (initial series or booster) before the start of study drug administration, day 1 of the study and the events associated with day 1, should not occur until at least 1 week after any COVID-19 vaccination dosing.

COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least 1 week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 3.

Table 3: 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		

9.1.1. Footnotes for the Schedule of Events

1. All screening-related procedures and assessments should be performed between day -85 to -1. During this window, rescreening is allowed up to 1 time. Patients cannot be rescreened based on skin testing or sIgE to cat not meeting eligibility. Baseline period assessment for symptom and medication requirements may not be repeated if patients do not meet eligibility criteria.
2. The baseline assessment period is up to 21 days, and should be completed for a minimum of 15 consecutive days during the approximately 12-week screening period. This period is utilized to demonstrate that patients are sufficiently symptomatic due to cat exposure while taking study provided standard of care anti-allergy rescue medications in standard therapeutic doses. Patients will complete an e-diary to record their nasal, ocular and asthma symptoms as well as anti-allergy rescue medication use during up to a 3-week period during screening. Patients will be required to be have experienced allergic rhinoconjunctivitis symptoms and to have used their anti-allergy rescue medications, as specified, for at least 8 days of a consecutive 15-day period during this time. Patients must meet a daily total rhinitis and conjunctivitis symptom threshold of at least 8 of 18 on at least 8 days of the consecutive 15-day baseline assessment period and use standard therapeutic doses of anti-allergy rescue medications on 8 of the consecutive 15 days during the baseline assessment period. If missing data are reported due to documented e-diary malfunction (eg, technical issues that are reported to the vendor), then the baseline assessment period may be extended accordingly, allowing the 15-day period to be re-started, to ensure that a consecutive 15 day period can be obtained. In such a circumstance, the medical monitor should be consulted, and agreement must be obtained with the sponsor.
3. Screening skin prick test for cat hair and skin prick test for other relevant allergens (such as house dust mite [HDM] and other relevant allergens) is performed as described in the study manual. If screening skin prick test for cat hair is negative at screening visit 1 (mean wheal diameter less than at least 5 mm greater than a negative control), then other screening visit 1 procedures do not need to be performed as the patient will have failed screening based upon cat hair skin prick testing (eg, perform skin prick testing prior to other procedures such as blood draw, spirometry, etc). Appropriate measures will be taken to prevent accidental unblinding during the treatment period when skin prick tests are performed.
4. 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.
5. Patients will remain in the clinic for 2 hours post-drug administration after receiving the first dose of study drug and after all subsequent doses.
6. All patients will undergo in-clinic spirometry during screening and at randomization. After randomization, spirometry will only be done in patients with asthma. Washout of bronchodilator medications will be discussed by investigator with the patient and verified before performing the measurements as specified in Section 9.2.2.10. During the treatment period, at a visit for which study drug dosing is scheduled, any patient with asthma

experiencing an asthma exacerbation and/or has a clinically relevant decrease in FEV1 ≥20% below baseline will not be dosed, per investigator judgement. In this case, the patient may return to the clinic within the permitted dosing window to be re-assessed for eligibility to receive study drug.

7. Only in patients with asthma: ANSD, ADSD, nighttime awakenings, asthma rescue medication use, ACQ-5, and post-randomization spirometry assessments will be collected.
8. For all in-clinic visits where study drug is administered at visit 3, visit 6, visit 8, visit 10, and visit 12 vital signs are taken twice: (1) prior to study drug administration, and (2) at approximately 2 hours after completion of the injections.
9. On day 1 and at subsequent visits, urine pregnancy test is completed prior to administration of study drug in women of childbearing potential. Postmenopausal women do not need urine pregnancy testing. If a urine pregnancy test is positive, a serum pregnancy test should be sent for confirmation. Drug should not be administered if a patient has a positive test.
10. FSH test to be performed in postmenopausal women only, if postmenopausal status is in question.
11. PK and ADA samples are to be collected prior to study drug administration. In the event of suspected AESIs, such as anaphylaxis or systemic hypersensitivity, additional samples for PK and ADA analyses may be collected as close to the event as practically possible.
12. Genomic analysis is optional for all patients enrolling in the study. One DNA sample is to be collected on day 1/randomization, but if this sample collection was omitted at baseline, it can be collected at any subsequent visit.
13. Assessments and procedures at unscheduled visits are to be performed at the discretion of the principal investigator.

9.1.2. Early Termination Visit

Patients who permanently discontinue study drug but who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule (Table 3). Patients who are withdrawn from the study will be asked to return to the clinic for Early Termination assessments only.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

All study procedures should be performed and/or collected at time points according to Table 3. For adolescent patients, parent(s)/caregiver(s) may assist in filling out questionnaires as needed.

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed only at screening/baseline to determine study eligibility or to characterize the baseline population: demographics, medical history, ECG, SPT for other allergens, and FSH determination (in postmenopausal women if postmenopausal status is in question).

9.2.2. Efficacy Procedures for All Patients

9.2.2.1. Total Nasal Symptom Score

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.

9.2.2.2. Total Ocular Symptom Score

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.

9.2.2.3. Total Symptom Score

The TSS is calculated by adding the TNSS (see Section 9.2.2.1) and TOSS (see Section 9.2.2.2) together, for a combined TSS of 0 to 18.

9.2.2.4. Daily Medication Score

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).

9.2.2.5. Combined Symptom and Medication Score

The CSMS is defined as TSS (see Section 9.2.2.3) plus DMS (see Section 9.2.2.4).

9.2.2.6. Standardized Rhinoconjunctivitis Quality of Life Questionnaire 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.

9.2.2.7. Patient Global Impression of Severity

The PGIS assesses the severity of the cat allergy symptoms over the past 1 week. Symptom severity ranges from 0 (no symptoms), 1 (mild), 2 (moderate), and 3 (severe) symptoms.

9.2.2.8. Patient Global Impression of Change

The PGIC assesses the overall change in cat allergy symptoms since the start of taking the study injection. It is measured with a 7-point Likert-type response scale, with values ranging from 0 = “Very Much Better” to 6 = “Very Much Worse”.

9.2.2.9. 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 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 is defined as a mean wheal diameter of at least 3 mm greater than a negative control.

Allergen exposure can induce immediate or late allergic reactions, such as allergic conjunctivitis, allergic rhinitis, asthma symptoms, or rarely anaphylaxis, in sensitized patients, which will be treated appropriately at the discretion of the investigator. With the exception of severe or clinically concerning reactions (as judged by the investigator), rescue treatments should be given after study endpoint data collection is obtained (eg, after the skin wheals are measured after application of allergen).

Starting at week 12, the SPTs will be performed in a manner to prevent accidental unblinding. The skin prick tests (cat, saline, histamine, and house dust mites) will be run in replicate (8 total) with a blinded code. The allergen wells will be blinded by the unblinded pharmacist (or qualified designee) and provided with labels (allergen #1 to allergen #7) to the blinded personnel (described in Section 8.6). One positive control histamine skin prick test will not be blinded.

Specific medications to be withheld prior to SPT are described in Prohibited Medications (Section 8.9.1).

9.2.2.10. 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 by the site investigator, will be performed locally during the study at specified time points (Table 3). Spirometry details will be available in a separate operational manual provided to the sites.

Spirometry will be performed in-clinic at screening and randomization for all patients to exclude any patients with abnormal lung function and/or poorly controlled asthma. FEV1 eligibility criteria

are specified in exclusion criteria (Section 7.2.2). After randomization, spirometry will only be done in patients with co-morbid asthma.

Spirometry will be performed after a washout period of bronchodilators according to their action duration to avoid interference with spirometry assessments and the investigator will discuss this with the patients. Examples of washout periods that investigator can discuss with the patient include withholding the last dose of short acting bronchodilator (SABA, such as salbutamol/albuterol or levosalbutamol/levalbuterol) for at least 6 hours, long acting bronchodilator (LABA, such as formoterol or salmeterol) for at least 12 hours, ultra-long-acting LABA (such as vilanterol, indacaterol) for at least 24 hours, short acting muscarinic antagonist (SAMA, such as ipratropium) for at least 8 hours, and long acting muscarinic antagonist (LAMA, such as tiotropium, umeclidinium) for at least 24 hours. Withholding times will be verified before performing the measurements.

9.2.2.11. Evaluation of Cat Exposure

Patients will be asked about their exposure to cat(s) at study visits as outlined in Table 3. From week 48 through week 60, as part of the patient reported e-diary, patients will be asked to report exposure to their cat(s). At the screening, baseline, and randomization visits, exposure to cat(s) is assessed via the inclusion/exclusion criteria.

9.2.2.12. Patient Experience Assessment

Patients will complete questions at week 60 (Table 3) to assess various parameters that may impact efficacy assessments. Questions will assess changes that patients experienced over the course of the study regarding the amount of time spent with their cat(s) and the impact on their perceived health status.

9.2.3. Efficacy Procedures for Patients with Asthma

9.2.3.1. 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’).

9.2.3.2. 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’).

9.2.3.3. 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').

9.2.3.4. Nighttime Awakenings

Only for patients with asthma, patients will report the number of nighttime awakenings by completing the e-diary every morning.

9.2.3.5. Rescue Medication Use

Only for patients with asthma, patients will report the number of rescue medication puffs (example- short-acting bronchodilator) by completing the e-diary every evening.

9.2.3.6. 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.

9.2.4. Safety Procedures for All Patients

9.2.4.1. Body Weight

Body weight will be assessed using calibrated scales. Body weight will be recorded to the nearest 0.1 kg.

9.2.4.2. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration, will be collected predose.

9.2.4.3. Physical Examination

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.

9.2.4.4. Electrocardiogram

A standard 12-lead ECG will be performed. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.4.5. Laboratory Testing

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

Patients will be tested for FSH levels (if postmenopausal status is in question) and will undergo serum and urine pregnancy testing (women of childbearing potential only); pregnancy testing is not required of women confirmed to be menopausal. Samples will be collected for quantitative assessment of allergen specific IgE.

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

Criteria for reporting laboratory values as an adverse event (AE) are provided in Section 10.1.1.

9.2.5. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in Table 3.

9.2.6. Immunogenicity Measurements and Samples

Samples for ADA assessment for REGN1908 and REGN1909 will be collected at time points listed in Table 3. Anti-REGN1908 and anti-REGN1909 neutralizing antibody (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. Detailed instructions for blood sample collection are included in the laboratory manual provided.

9.2.7. Pharmacodynamic and Exploratory Biomarker Procedures

Blood samples will be obtained for additional exploratory research to better understand the effects of various anti-Fel d 1 antibodies on cat allergy. This will include the assessment of effective competition between REGN1908 and REGN1909 (either alone or in combination) and endogenous sIgE in serum for allergen binding in an in vitro interference/ inhibition assay.

These results will be part of exploratory research analysis and will be included in an exploratory biomarker report, which will not be described in the clinical study report.

9.2.8. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.9. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points according to Table 3. DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of cat allergy and related diseases. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN1908-1909 treatment, cat allergy or related allergic diseases, clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of cat allergy as well as related allergic diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or cat allergy and related diseases.

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

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of on-treatment period (see Section 11.4.6.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Although not considered an adverse event, if a pregnancy occurs during the study, information about the progress and outcome of the pregnancy will be collected. This should include the date that the subject became pregnant, information about the health of the subject, any medication treatments received during the pregnancy, any medical problems affecting or related to the pregnancy and/or the baby, whether the pregnancy came to term, the date of the child's birth, and the health of the child after birth. To collect this information, the study staff should contact the subject every trimester for updates on the pregnancy. The subject should also be asked to contact the site as soon as possible in the event of any medical problem affecting or related to the pregnancy and/or baby. Once the baby is born, the study staff will ask for a final update after one well-baby visit with the pediatrician.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (SAE; diagnosis or symptom requiring hospitalization). A procedure

is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE case report form (CRF). Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious): Adverse events of special interest for this study include the following:
  - Severe or systemic hypersensitivity reactions

    NOTE: Anaphylaxis will be prospectively analyzed using the criteria discussed in the statement paper from the Second Symposium on the definition and Management of Anaphylaxis (Sampson, 2006)
  - Asthma exacerbations, defined as asthma symptoms requiring treatment with systemic corticosteroids or resulting in an emergency room visit or hospitalization
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification,

any pregnancy occurring in a female during the study or within 24 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. 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.

10.2.4. Severity

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

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

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

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

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

Injection Site Reactions

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

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

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

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

10.2.5. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term

- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

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

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Institutional Review Boards (IRBs)/Ethics Committees (ECs), and the participating investigators of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the active study drug (REGN1908-1909), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (REGN1908-1909) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRB/EC as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Handling of missing data due to the COVID-19 pandemic and any additional analyses required to investigate the impact of COVID-19 to understand estimated treatment effect and safety will be detailed in the SAP.

11.1. 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 significantly different in patients receiving REGN1908-1909 and placebo.

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

11.2. Justification of Sample Size

The sample size will be approximately 315 patients per arm, for a total of 630 patients. 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 average CSMS 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 0.05 was assumed. 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 4.

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 (Demoly, 2016) 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.

Table 4: Summary of Statistical Assumptions and Power for Selected Secondary Endpoints

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

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 PBO 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.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

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.

11.3.2. Safety Analysis Set

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

11.3.3. Pharmacokinetic Analysis Sets

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

11.3.4. Immunogenicity Analysis Sets

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

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or positive for ADA with at least 1 non-missing result in the NAb assay (patients who are ADA negative are set to negative in the NAb analysis set).

11.4. Statistical Methods

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

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of randomized patients who discontinue the study, and the reasons for discontinuation
- The total number of randomized patients who discontinued from study treatment, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

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

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary endpoint, the daily CSMS averaged over the last 12 weeks of the treatment period (weeks 48 to 60), will be analyzed on the full analysis set (FAS), which consists of all randomized patients.

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, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed effects and the baseline CSMS as a covariate. The least squares 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.

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 daily total nasal symptom scores (TNSS, max score 12/day), daily TOSS (max score 6/day) and daily medication scores (DMS, max of 20/day) recorded over the last 12 weeks of the treatment period (weeks 48 to 60).

Any data collected after rescue medication use will be used in the analysis for the CSMS. Since the relevant prohibited medication use may have an impact on symptom measurements, the CSMS data will be set to missing at the time of and after receiving the prohibited medication. The details of the relevant prohibited medications will be specified in the SAP. The primary estimand will

utilize the CSMS calculated by observed components prior to receiving relevant prohibited medication or the worst score of all observations in corresponding treatment group if a patient has no single value of CSMS during the last 12 weeks of the treatment period (composite strategy).

If a patient has no single available value of CSMS during the last 12-week assessment period, a hybrid approach of the worst score and the multiple imputation (MI) will be used to impute the missing data for the primary analysis. Missing data because of patients' discontinuation from study due to AEs and lack of efficacy will be imputed using the worst score of all the observations in corresponding treatment group, and multiple imputation (MI) will be applied to impute missing values due to all other reasons. With respect to the missing data handling of daily entries, sensitivity analyses may be performed to confirm robustness of the conclusion drawn based on the main model for primary analysis. Details of these sensitivity analyses will be provided in the SAP.

The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimand for the primary endpoint are summarized in Table 5.

Table 5: Summary of Estimand for Primary Endpoint

	Estimand			
Endpoint Category	**Endpoint(s)**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary endpoint – Continuous	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: • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) • Rescue treatment to treat allergic symptoms during the efficacy assessment period: data after rescue medication will be used in the analysis (treatment policy strategy) • Relevant prohibited medications taken during the efficacy assessment period: the daily average CSMS will be calculated by observed components prior to receiving prohibited medication or the worst score of all observations in corresponding treatment group if a patient has no single value of CSMS during the last 12 weeks of the treatment period (composite strategy) In addition, if a patient has no available values of CSMS during the last 12 weeks of the treatment period, the missing data imputation rules are as follows: • Missing data because of patients' discontinuation from study due to AEs and lack of efficacy will be	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

Endpoint Category	Estimand			
	Endpoint(s)	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
			imputed using worst score of all the observations in corresponding treatment group (largest number) and missing data due to any other reason will be imputed using multiple imputation (MI).	

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint with respect to age group, gender, region, and other factors that will be specified in the SAP.

11.4.3.2. Secondary Efficacy Analysis

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

The average symptom score or medication score over the initial or last 12 weeks of the treatment period will be calculated in similar way as the primary endpoint.

The intercurrent events, strategies, and the corresponding missing data handling approaches for the estimands for key secondary endpoints and selected other secondary endpoints are summarized in Table 6.

Table 6: Summary of Estimands for Key Secondary Endpoints and Selected Other Secondary Endpoints

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Secondary endpoint – Continuous, daily measurements	Daily TNSS, TSS, TOSS, and DMS over the last 12 weeks of the efficacy assessment period (weeks 48 to 60) and the percent change from baseline in these endpoints Daily TNSS, CSMS, TSS, DMS, and TOSS over the initial 12 weeks of the efficacy assessment period (weeks 0 to 12) and the percent change from baseline in these endpoints	FAS	The intercurrent events will be handled as follows: • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) • Rescue treatment to treat allergic symptoms during the efficacy assessment period: data after rescue medication will be used in the analysis (treatment policy strategy) • Relevant prohibited medications taken during the efficacy assessment period: the daily average symptom or medication score will be calculated by observed score prior to receiving relevant prohibited medication or the worst score of all observations in corresponding treatment group if a patient has no single value of the score during the 12-week assessment period (composite strategy). In addition, if a patient has no available values of the relevant measurement during the 12-week assessment period, the missing data imputation rules are as follows: • Missing data because of patients' discontinuation from study due to AEs and lack of efficacy will be imputed using the worst score of all the observations in corresponding treatment group and missing data due to any other reason will be imputed using MI.	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
Secondary endpoint – Continuous, SPT	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	FAS	The intercurrent events will be handled as follows: • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) • Rescue treatment to treat allergic symptoms during the efficacy assessment period: data after allergy-relieving rescue medication will be used in the analysis (treatment policy strategy) • Relevant prohibited medications taken during the defined window leading up to SPT at the relevant visit (week 12 or week 60): data prior to receiving prohibited medication or the worst value of all observations in corresponding treatment group if a patient has no single value of the value during the 12-week assessment period (composite strategy) will be utilized. In addition, if a patient has no available values of the relevant measurement during the 12-week	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

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
			assessment period, 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 and missing data due to any other reason will be imputed using MI.	
Secondary endpoint – Continuous, FEV1	Percent change from baseline to week 12 FEV1 Percent change from baseline to week 60 FEV1	All randomized patients with asthma	The intercurrent events will be handled as follows: • Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy) • Rescue treatment to treat allergic symptoms during the efficacy assessment period: data after rescue medication will be used in the analysis (treatment policy strategy) • Relevant prohibited medications taken during the defined window leading up to spirometry at the relevant visit (week 12 or week 60): data prior to receiving prohibited medication or the worst value of all observations in corresponding treatment group if a patient has no single value of the score during the 12-week assessment period (composite strategy) will be utilized. In addition, if a patient has no available values of the relevant measurement during the 12-week assessment period, 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 and missing data due to any other reason will be imputed using MI.	ANCOVA model with treatment group, stratification factors, and cat sIgE (<17.5 kUa/L versus ≥17.5 kUa/L) as fixed factors and baseline FEV1 measurement as a covariate

11.4.4. Control of Multiplicity

Multiplicity is considered for testing multiple endpoints. The overall type-I error rate will be controlled at the 2-sided 0.05 level.

A non-binding futility interim analysis (IA) is planned in this study (details are provided in Section 6.2), 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.

At the final analysis, a hierarchical testing procedure is proposed to strongly control the family wise type-I error rate for testing the primary and key secondary endpoints. Two-sided alpha of

0.049 will be allocated to the endpoints. The detailed hierarchical order will be specified in the study SAP.

11.4.5. Timing of Statistical Analyses

A non-binding futility IA will be performed when at least 40% of all randomized patients complete week 12 or discontinue before week 12. The IA will be performed by independent statisticians who support the IDMC and who are separate from personnel involved in the trial conduct.

The unblinded primary analysis will be performed when all randomized participants have completed the last 12 weeks of the treatment period (week 60). This unblinded primary analysis will be considered the final analysis for the efficacy endpoints. Additional data between this database lock and last patient completing the last visit will be summarized in a CSR.

11.4.6. Safety Analysis

The analysis population for the safety endpoints (SAF) includes all randomized patients who receive at least 1 injection of study drug and will be analyzed according to the intervention they actually received. The SAF will be the basis for the analyses for the study period. The safety analyses will be based on descriptive statistics using the observed data. The number and percentage of patients with at least 1 treatment-emergent adverse event (TEAE), treatment-emergent SAE, treatment-emergent AESI, treatment-related TEAE, and TEAE leading to treatment discontinuation will be tabulated by treatment group. Descriptive statistics of values and change from baseline values for each laboratory and vital signs parameters will be summarized by treatment group at each time point. The number and percentage of patients with at least 1 incidence of potentially clinically significant abnormality at any time during the treatment-emergent period will be summarized by treatment group.

The SAP for the study will be developed and finalized before database lock. Statistical analyses were conducted with SAS software version 9.4 or above.

11.4.6.1. Adverse Events

Definitions

For safety variables, 3 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 (weeks 0 to 60).
- 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 (weeks 60 to 72).

Treatment-emergent adverse events 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.

Adverse events of special interest (Section 10.2.3 and Section 10.1.3) for this study include:

- Severe or systemic hypersensitivity reactions defined using the narrow SMQ for hypersensitivity, with manual adjudication of relevant PTs by medical monitor before database lock.
- Asthma exacerbations defined using the narrow SMQ for asthma and further manually adjudicated for events requiring treatment with systemic corticosteroids or resulting in an emergency room visit or hospitalization.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by system organ class (SOC) and preferred term (PT)
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- Treatment related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized by treatment group.

Safety AE outcomes such as time to the first AESIs or TEAE leading to permanent treatment discontinuation, will be assessed by Kaplan-Meier estimates (K-M plot). In order to detect any AE signals, the hazard ratio (HR) will 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.

11.4.6.2. Other Safety

Vital Signs

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

Laboratory Tests

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

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

11.4.6.3. Treatment Exposure

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

- (date of last dose of study drug in the specific study part – date of first dose of study drug in the specific study part) + 84 days

In addition, duration of cumulative exposure to REGN1908-1909 across study parts will be calculated as follows:

- (date of last dose of study drug – date of first dose of study drug in the study) + 84 days.

Number and percentage of patients exposed to study drug will be summarized by time periods of specific lengths for each treatment group. The lengths of interest will be specified in the SAP.

In addition, duration of exposure will be summarized as a continuous variable for each treatment group with the number of patients reflected in the calculation (n), mean, median, SD, minimum, the first and third quartiles, and maximum.

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

11.4.7. Pharmacokinetics

11.4.7.1. Analysis of Drug Concentration Data

The concentrations of total REGN1908 and total REGN1909 over time will be summarized by descriptive statistics for each of the treatment groups.

No formal statistical hypothesis testing will be performed.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response, titer, and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

- NAb status for samples that are positive in the ADA assay

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers and NAb positivity presented by patient, time point, and dose will be provided separately for REGN1908 and REGN1909. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated separately for REGN1908 and REGN1909. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.4.9. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Biomarker results will be summarized by baseline, measured values, change from baseline, and percent change from baseline to each scheduled assessment time point with descriptive statistics.

11.4.10. Analysis of Quality of Life Data

Quality of life data will be analyzed using the same method as specified for the continuous secondary efficacy variables.

11.5. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

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

12.1.2. Electronic Systems

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

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

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

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

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

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

12.2.3. Case Report Form Requirements

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

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

For adolescent patients, local law must be observed in deciding whether the consent of 1 or both parents/guardians is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB or EC and in accordance with the local regulations and requirements.

Patients/parents/guardians who can write but cannot read will have the ICF/IAF read to them before signing and dating the ICF/IAF.

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

The original ICF/IAF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the adult patient, or to the adolescent patient and his/her parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF/IAF must be reviewed and updated appropriately. All study patients (and adolescent patients' parent[s] or legal guardian[s]) must be informed of the new information and provide their written consent/assent if they wish to continue in the study. The original signed revised ICF/IAF must be maintained in the patient's study record and a copy must be given to the adult patient, and the adolescent patient and his/her parent(s) or legal guardian(s).

13.3. Patients Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

Arbes SJ, Gergen PJ, Vaughn B,Zeldin DC. Asthma cases attributable to atopy: Results from the Third National Health and Nutrition Examination Survey. Journal of Allergy and Clinical Immunology 2007; 120(5):1139-1145.

Bateman BJ,Dean TP. The Cheshire cat's grin--is cat allergy here to stay? Clin Exp Allergy 1999; 29(6):725-728.

Bielory L, Katelaris CH, Lightman S,Naclerio RM. Treating the ocular component of allergic rhinoconjunctivitis and related eye disorders. MedGenMed 2007; 9(3):35.

Blaiss MS, Hammerby E, Robinson S, Kennedy-Martin T,Buchs S. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: A literature review. Ann Allergy Asthma Immunol 2018; 121(1):43-52 e43.

Bollinger M, Eggleston P, Flanagan E,Wood R. Cat antigen in homes with and without cats may induce allergic symptoms†. Journal of Allergy and Clinical Immunology 1996; 97(4):907-914.

Bollinger ME, Wood RA, Chen P,Eggleston PA. Measurement of cat allergen levels in the home by use of an amplified ELISA. Journal of Allergy and Clinical Immunology 1998; 101(1):124-125.

Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G,World Health O. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108(5 Suppl):S147-334.

Calderon MA, Bernstein DI, Blaiss M, Andersen JS,Nolte H. A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. Clin Exp Allergy 2014; 44(10):1228-1239.

Chapman MD,Wood RA. The role and remediation of animal allergens in allergic diseases. J Allergy Clin Immunol 2001; 107(3 Suppl):S414-421.

Ciprandi G, Incorvaia C, Scurati S, Puccinelli P, Soffia S, Frati F, et al. Patient-related factors in rhinitis and asthma: the satisfaction with allergy treatment survey. Current Medical Research and Opinion 2011; 27(5):1005-1011.

Coren S. Allergic patients do not comply with doctors' advice to stop owning pets. Bmj 1997; 314(7079):517.

Demoly P, Emminger W, Rehm D, Backer V, Tommerup L,Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016; 137(2):444-451.e448.

Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012; 129(3):717-725.e715.

Durham SR,Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol 2016; 137(2):339-349.e310.

Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol 2020; 146(4):721-767.

FDA. Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA. 2009; US Department of Health and Human Services Food and Drug Administration.

Gentile D, Bartholow A, Valovirta E, Scadding G,Skoner D. Current and future directions in pediatric allergic rhinitis. J Allergy Clin Immunol Pract 2013; 1(3):214-226; quiz 227.

Giavina-Bianchi P, Aun M, Takejima P, Kalil J,Agondi R. United airway disease: current perspectives. Journal of Asthma and Allergy 2016:93.

Gomes PJ. Trends in prevalence and treatment of ocular allergy. Curr Opin Allergy Clin Immunol 2014; 14(5):451-456.

Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019; 200(8):e70-e88.

Grönlund H, Saarne T, Gafvelin G,van Hage M. The Major Cat Allergen, Fel d 1, in Diagnosis and Therapy. International Archives of Allergy and Immunology 2009; 151(4):265-274.

Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 2009; 64(10):1498-1506.

Humane Society of United States. Pets by the numbers (APPA survey). https://humanepro.org/page/pets-by-the-numbers. Published 2021. 2021.

Izquierdo-Domínguez A, Valero AL,Mullol J. Comparative analysis of allergic rhinitis in children and adults. Curr Allergy Asthma Rep 2013; 13(2):142-151.

James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. Journal of Allergy and Clinical Immunology 2011; 127(2):509-516.e505.

Karlsson AS, Renstrom A, Hedren M,Larsson K. Allergen avoidance does not alter airborne cat allergen levels in classrooms. Allergy 2004; 59(6):661-667.

Kleine-Tebbe J, Kleine-Tebbe A, Jeep S, Schou C, Løwenstein H,Kunkel G. Role of the Major Allergen Fel d I in Patients Sensitized to Cat Allergens. International Archives of Allergy and Immunology 1993; 100(3):256-262.

Krishnan JA, Cloutier MM,Schatz M. National Asthma Education and Prevention Program 2020 Guideline Update: Where Do We Go from Here? Am J Respir Crit Care Med 2021; 203(2):164-167.

Kündig TM,Bachmann MF. Allergen-specific immunotherapy: Regulatory T cells or allergen-specific IgG? Human Vaccines 2010; 6(8):673-675.

Leung DYM, Sampson HA, Geha R,Szefler SJ. *Preface*. Pediatric Allergy: Principles and Practice. Elsevier; 2010: ix.

Mounsey AL,Gray RE. Topical Antihistamines and Mast Cell Stabilizers for Treating Allergic Conjunctivitis. Am Fam Physician 2016; 93(11):915-916.

Niesler A, Ścigała G,Łudzeń-Izbińska B. Cat (Fel d 1) and dog (Can f 1) allergen levels in cars, dwellings and schools. Aerobiologia 2016; 32(3):571-580.

Olivieri M, Heinrich J, Schlünssen V, Antó JM, Forsberg B, Janson C, et al. The risk of respiratory symptoms on allergen exposure increases with increasing specific IgE levels. Allergy 2016; 71(6):859-868.

Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. Nature Communications 2018; 9(1).

Perzanowski MS, Ronmark E, James HR, Hedman L, Schuyler AJ, Bjerg A, et al. Relevance of specific IgE antibody titer to the prevalence, severity, and persistence of asthma among 19-year-olds in northern Sweden. Journal of Allergy and Clinical Immunology 2016; 138(6):1582-1590.

Riedi CA,Rosario NA. Prevalence of allergic conjunctivitis: a missed opportunity? Allergy 2010; 65(1):131-132.

Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2011; 127(5):1226-1235.e1227.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117(2):391-397.

Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen

Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. Jama 2017; 317(6):615-625.

Shi R,Derendorf H. Pediatric Dosing and Body Size in Biotherapeutics. Pharmaceutics 2010; 2(4):389-418.

Temrikar ZH, Suryawanshi S,Meibohm B. Pharmacokinetics and Clinical Pharmacology of Monoclonal Antibodies in Pediatric Patients. Paediatr Drugs 2020; 22(2):199-216.

The European Pet Food Industry. European Facts & Figures. https://fediaf.org/images/FEDIAF_facts_and_figs_2019_cor-35-48.pdf. Published 2019. 2021.

van Ree R, van Leeuwen WA, Bulder I, Bond J,Aalberse RC. Purified natural and recombinant Fel d 1 and cat albumin in in vitro diagnostics for cat allergy. Journal of Allergy and Clinical Immunology 1999; 104(6):1223-1230.

Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clinical & Experimental Allergy 2011; 41(9):1177-1200.

Wood RA, Chapman MD, Adkinson NF, Jr.,Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989; 83(4):730-734.

Xu Y, Langevin BA, Zhou H,Xu Z. Model-Aided Adults-to-Children Pharmacokinetic Extrapolation and Empirical Body Size-Based Dosing Exploration for Therapeutic Monoclonal Antibodies-Is Allometry a Reasonable Choice? J Clin Pharmacol 2020; 60(12):1573-1584.

Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy 2010; 65(12):1525-1530.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: 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 and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study 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

Protocol Number: R1908-1909-ALG-2102

Protocol Version: R1908-1909-ALG-2102 Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

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Sponsor's Responsible Clinical Study Lead

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Sponsor's Responsible Biostatistician

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