

EudraCT Number: 2018-002477-22

Regeneron Pharmaceuticals, Inc.

**Clinical Study Protocol****STUDY TITLE**

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study in Cat-Allergic Patients with Asthma to Evaluate the Efficacy of a Single Dose of REGN1908-1909 to Reduce Bronchoconstriction Upon Cat Allergen Challenge

**Compound:** REGN1908-1909**Clinical Phase:** 2**Protocol Number:** R1908-1909-ALG-1703**Protocol Version:** R1908-1909-ALG-1703 Amendment 2**Amendment 2 Date of Issue:** *See appended electronic signature page***Amendment 1 Date of Issue:** 18 Dec 2018**Original Date of Issue:** 16 Aug 2018**Medical /Study Director:** [REDACTED]

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## AMENDMENT HISTORY

### Amendment 2

The following changes have been made based on operational considerations and input from investigators. The table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Clarified that asthmatic and allergic symptoms that occur in response to the environmental exposure unit (EEU) are not to be reported as adverse events (AEs), as they will be recorded as outcome measures. However, AEs that occur in response to allergen exposure in the EEU that are outside of expected symptoms, including events which qualify as serious adverse events (SAEs), up to 24 hours after EEU should be reported as AEs and SAEs as applicable.	Section 9.4.1 Adverse Events
Clarified that if patients have a screening asthma control test (ACT) <20 at any screening visit, they may be rescheduled after asthma control improves (eg, if patient has transient upper respiratory tract infection or exposure to natural allergens). Patients who are rescheduled must demonstrate stable asthma control by having an ACT $\geq 20$ at 2 consecutive visits, separated by at least a week.	Section 6.2.2 Exclusion Criteria, #30
Clarified that forced expiratory volume (FEV1) will be monitored at home for approximately 18 hours after leaving the clinical unit and if there is a 30% (changed from 15%) drop in FEV1, the investigator(s) will receive an alarm by email to inform about the change in spirometry and the patient will be contacted and evaluated by the medical doctor. A 15% drop is expected with a late asthmatic response and therefore does not require an email message, whereas a 30% drop is considered a significant clinical change. FEV1 will be monitored at home using a portable hand-held spirometer for approximately 18 hours after leaving the clinical unit (a total of 24 hours of monitoring from the end of the EEU exposure).	Section 1 Introduction Section 7.4 Management of Acute Reactions Section 10.4.3.4 Timing of Analyses
Added that patient reported history (for at least 2 years) of symptomatic cat allergen-triggered asthma will be collected.	Section 6.2.1 Inclusion Criteria, #2
Clarified that randomization/study drug administration must occur within 14 to 28 days from screening and that the cat allergen challenges in the EEU are separated by at least 21 days.	Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #2
Added “This will be the final analysis of the primary endpoint” to the First Step Analysis section, where the first-step analysis may be performed when the last patient completes day 8 of the treatment period and has undergone the Cat Allergen Challenge in the EEU at day 8.	

Change and Rationale for Change	Section Changed
Added that additional spirometry may be performed when prompted by asthma symptoms and included further procedural details regarding how spirometry is conducted during the study.	Section 8.2.2.4 Spirometry Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #5
Clarified that postmenopausal women do not need FSH testing unless required to confirm their postmenopausal status. Pregnancy testing is not required for women with bilateral oophorectomy	<a href="#">Clinical Study Synopsis: Procedures and Assessments</a> Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.3.6 Laboratory Testing <a href="#">Table 1 Schedule of Events</a> Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #16, #26 e
Added that in patients who receive EEU related medications (including medications given on-site and rescue medications taken at-home), the impact of the carryover of medications between challenges will be explored.  Added that the time course of asthma response comprising early asthmatic response (EAR) and late asthmatic response (LAR) will be visualized and summarized	Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary Efficacy Analysis
Procedural clarifications were added regarding the timing of the titrated skin prick test (SPT), vital signs measurements, physical examinations, spirometry, minute ventilation, fractional exhaled nitric oxide (FeNO) measurement, collection of nasal brushing samples, randomization, screening visits 1 and 2, as well as replacement of patients.	Section 6.4 Replacements of Patients <a href="#">Table 1 Schedule of Events</a> Section 8.2.2.4 Spirometry Section 8.1.1 Footnotes for the Schedule of Events Table, Footnotes #2, #5, #6, #8, #9, #20, #25 (new), #26 (new), #27 (new)
Clarified that rescue treatment kit medications, taken at home within 24 hours from the EEU exposure will not be considered concomitant medications. Rescue medications taken from the kit within 24 hours of EEU exposure will be collected separately.	Section 7.8 Concomitant Medications
Updated language per current protocol template.	Section 2.3.3 Exploratory Immunogenicity Objective Section 4.5 Immunogenicity Variables Section 6.2.2 Exclusion Criteria #26.e

Change and Rationale for Change	Section Changed
Modifications for consistency and clarity, and administrative updates.	<a href="#">Clinical Study Synopsis</a> : Objectives, Study Design Section 1 Introduction Section 3.2.4 Rationale for Endpoints Section 4.6 Pharmacodynamic and Other Biomarker Variables Section 7.6 Method of Treatment Assignment Section 7.8.1 Prohibited Medications <a href="#">Table 1</a> Schedule of Events: Minute Ventilation row Section 8.2.6.1 Biomarkers Section 8.2.7.1 Genomics Study-(Mandatory) Section 9.4.4 Reporting Adverse Events Leading to Withdrawal from the Study Section 10.3.3 Pharmacokinetic Analysis Set Section 10.4.3.4 Timing of Analyses Section 10.4.5.1 Analysis of Drug Concentration Data Section 10.5 Interim Analysis Section 10.6 Additional Statistical Data Handling Conventions
Correction of typographical, grammatical, and formatting errors	Throughout the protocol

## Amendment 1

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

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>The following exploratory objectives are added as they were inadvertently excluded from the previous version of the protocol:</p> <ul style="list-style-type: none"> <li>• To assess the prophylactic effect of REGN1908-1909 on TNSS, TOSS, and chest symptoms up to 24 hours after leaving the EEU</li> <li>• To assess the extent of REGN1908-1909 interference with the measurement of endogenous anti-Fel d1 IgE in baseline samples and its relationship to clinical benefit</li> </ul>	Section 2.3.1 Exploratory Objectives
<p>The design rationale has been revised to clarify the length of serious adverse event follow-up as per a Health Authority request:</p> <p>The follow-up period of 16 weeks (12-week assessment period and then a 4-week safety follow-up) after the single dose of REGN1908-1909, plus an additional 30 days of follow-up for any investigational drug-related SAE that occurs after study completion, represents a follow-up period of approximately 5 months, which is within the 4 to 5 half-life window for antibody levels to fall to undetectable levels. Serious adverse events considered by the investigator to be related to the investigational product are to be reported even if onset is greater than 30 days from the end of study</p>	Section 3.2.1 Rationale for Study Design Section 5.1 Study Description and Duration
<p>The study flow diagram schema 1 has been revised to clarify the duration of the exposure period as 12 weeks followed by 4 weeks of follow-up as per the Health Authority request.</p>	Figure 1 Study Flow Diagram Schema 1
<p>A subclass of serum antibodies IgA, IgG1, and IgG2 will not be measured due to unavailability of the assay methods.</p> <p>Gene Expression Analysis of Type 2 Inflammation of Nasal Mucosa by RNAseq on day 85 biomarker sample will not be performed as the day 85 nasal brushing sample will not be collected.</p>	Section 4.6 Pharmacodynamic and Other Biomarker Variables Section 8.2.6.1 Biomarkers

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>Screening period is revised as -85 to -14 days.</p> <p>Clarified that the cat EEU visit 3 during screening must be at least 3 weeks from the cat EEU visit 6 (visits must be spaced apart by at least 3 weeks to avoid allergen priming). Previously the period of -85 to -1 did not account for the required necessary 3-week period between cat EEU visit 3 and cat EEU visit 6.</p> <p>Added the following clarification per the Ethics Committee request: The informed consent will be provided to the patient prior to visit 1 so that he/she has sufficient time to read the informed consent and to ask questions to the investigator.</p>	<p><a href="#">Study Synopsis</a></p> <p><a href="#">Section 5 Study Design</a></p> <p><a href="#">Section 5.1 Study Description and Duration</a></p>
<p>An Independent data monitoring committee will be assembled for the study and a IDMC section has been added to the protocol per the Health Authority request.</p>	<p><a href="#">Section 5.2.2 Independent Data Monitoring Committee</a></p>
<p>Protocol exit criteria updated as per the Health Authority feedback to provide explicit criteria for discontinuation as follows:</p> <ul style="list-style-type: none"> <li>• The patient experiences a FEV1 reduction <math>\geq 50\%</math> from the baseline measurement of FEV1 (before EEU exposure) at any time during the study</li> <li>• The patient requires emergency treatment of asthma or of a hypersensitivity reaction in a hospital or emergency room</li> <li>• The patient experiences a systemic allergic response and/or anaphylaxis requiring epinephrine</li> </ul>	<p><a href="#">Section 6.3 Premature Withdrawal from the Study</a></p>
<p>Misplaced criterion inadvertently written as an inclusion criterion and moved to the exclusion criteria section which is what was intended:</p> <p>Revised inclusion criterion #2e to now be exclusion criterion #30:</p> <p>Screening asthma control test (ACT) <math>&lt; 20</math> at any screening visits as higher scores are normal and lower scores suggest poorly controlled asthma</p>	<p><a href="#">Section 6.2.1 Inclusion criteria #2</a></p> <p><a href="#">Section 6.2.2 Exclusion Criteria #30</a></p>

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>Exclusion criterion #17 revised to remove the following text: “causing TNSS &gt;2” as this qualifier of significant rhinitis was confusing to the study site staff.</p> <p>Exclusion criteria #26 revised to clarify that the duration of the use of highly effective contraception methods is at least 6 months after the last dose of study drug in women of childbearing potential per the Health Authority request.</p> <p>Exclusion criterion #27 describing requirements for male contraception added to ensure consistency with the Investigator's Brochure language.</p>	Section <a href="#">6.2.2</a> Exclusion Criteria, #17, #26, and #27
<p>Added the following text to clarify the study activities in the case that the patient has received the 1 dose of study drug but who then opts out of study-related EEU challenges:</p> <p>Patients who opt out of EEU challenges after receipt of study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule except for EEU exposures and EEU related procedures (see Section <a href="#">8</a> )</p>	Section <a href="#">7.3.2</a> Study Drug Discontinuation
<p>Following text added in reference to the criteria for discharge from the unit to home per the Health Authority request:</p> <p>Otherwise, in case of FEV1 is &lt;90% of the baseline value, patients will continue to be monitored at the clinic until the patient meets criteria for discharge</p>	Section <a href="#">7.4</a> Management of Acute Reactions Section <a href="#">8.2.2.4</a> Spirometry
<p>The following text deleted; “Randomization will be stratified according to visit date”.</p> <p>In original study design, randomization was stratified such that the patients who are in the EEU together at the same time are equally allocated to drug and placebo; however, there were logistical difficulties in achieving this consistently throughout the study. As there are 4 Cat EEU visits after randomization, each with a visit window of <math>\pm 3</math> days, it is not possible to ensure that the group of patients who complete the Cat EEU visits together will be the same for each of the visits. Therefore, the randomization will not be stratified.</p>	Section <a href="#">7.5</a> Method of Treatment Assignment

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>Following clarifications added:</p> <p>Nasal brushing samples will be collected 6 hours from the start of the EEU challenge instead of after the EEU challenge. Phrase “from the start” was added.</p> <p>Nasal brushing sample collection frequency has been updated to eliminate sample collection at day 85.</p> <p>Currently, the induction of type-2 response in the nasal epithelium after chamber exposure has not yet been fully established. This would be the first time that Sponsor will test the gene expression changes as exploratory biomarkers post chamber exposure for cat dander. In previous studies for cat allergy with neutralizing antibodies (REGN1908-1909-ALG-1325), maximal suppression of clinical symptoms after nasal allergen challenge was observed on day 29 after dosing. Comparison of expression changes between baseline and day 29 provides the best opportunity to detect this inflammatory response and assess how these changes correlate with clinical response.</p>	Section 8.2.6.1 Biomarkers Section 2.3.1 Exploratory Efficacy Objectives
<p>Serum samples from patients obtained before drug exposure will be tested in an in-vitro competition assay to assess whether REGN1908-1909 can inhibit the binding of endogenous anti-fel-d1 IgE to the allergen</p>	Section 8.2.6.1 Biomarkers (Interference Assay with REGN1908-1909)
<p>Following clarification added:</p> <p>Serum allergen-specific IgE levels (cat hair, Fel d 1) will be measured at screening visit 1 and as described in schedule of events Table 1.</p>	Section 8.2.6.1 Biomarkers

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>Following edits/clarifications were done:</p> <p>Revised text: The challenge will not proceed if patients have a TNSS greater than 4, an asthma control test (ACT) score &lt;20 at any of the screening visits, or FEV1 of less than 70% of predicted value.</p> <p>Following text added in reference to the criteria for discharge from the unit to home per the Health Authority request:</p> <p>At the end of the 6-hour monitoring period, patients are discharged home if <math>FEV1 \geq 90\%</math> of the baseline value.</p> <p>In schedule of events table, screening days was revised to "-85 to -14" instead of days "-85 to -1" to clarify that cat EEU visit 3 and visit 6 must be spaced at least 3 weeks apart to prevent a priming effect of visit 3 on visit 6.</p> <p>Skin prick test with serial allergen titration (CAT SPT) will be performed at Cat EEU visit 3 instead of Cat EEU visit 2.</p> <p>Footnote #1 revised to add "-85 to -14"</p> <p>Footnote #5 revised as follows: FEV1 will be performed at baseline prior to entry into the EEU, every 10 minutes during the EEU exposure, every 30 minutes in the observation room for 6 hours after leaving the EEU, and then every hour for 18 hours after EEU exposure, except during sleeping.</p> <p>Footnote #6 revised as follows: TNSS, TOSS, and chest symptom questions are assessed prior to Cat Allergen Challenge, approximately every 20 minutes during the challenge in the exposure unit, every 1 hour for 6 hours post-challenge while patients are being observed in the observation room, and then every 2 hours up to 18 hours after EEU exposure, while they are home, except for the time that they are sleeping. Further details are provided in the study manual.</p> <p>"Fel d 1" deleted from footnote #4 as a skin prick test specific for Fel d 1 is currently not available.</p> <p>Footnote #7 clarified as follows: PNIF is assessed prior to Cat Allergen Challenge, approximately at the time of the EAR, and approximately 6 hours post-challenge while patients are being observed in the observation room. Further details are provided in the study manual.</p>	<p>Clinical Study Protocol - <a href="#">Synopsis: Study Design</a></p> <p>Section <a href="#">8.1.1</a> Footnotes for the Schedule of Events Table</p> <p><a href="#">Table 1: Schedule of Events</a></p> <p>Section <a href="#">5.1</a> Study Description and Duration</p>

Change and Rationale for Change (listed in numerical order by Section)	Section Changed
<p>Footnote#8 revised to add the following text: Titrated skin prick test will be performed prior to EEU exposure at all visits.</p> <p>Footnote #20 Following clarification added: Vital signs and spirometry will be collected once per hour. AEs will be collected during the observation period.</p> <p>Footnote #22 added to the Schedule of Events Table to clarify that blood draws should be performed before the EEU exposure</p> <p>Footnote #23 added to clarify that cat EEU visit 3 and visit 6 must be spaced at least 3 weeks apart to prevent a priming effect of visit 3 on visit 6.</p> <p>A new footnote #24 added as follows: Assessments and procedures at the unscheduled visit(s) are to be performed at the discretion of the principle investigator.</p> <p>Serum samples for specific IgE for Fel d 1 and cat hair will not be collected at early termination, end of study, and any unscheduled visits as there is no EEU exposure at these visits.</p> <p>Serum samples for sIgE (Fel-D 2, 4, 7) tests will not be collected at early termination, end of study, and any unscheduled visits as there is no EEU exposure at these visits.</p>	
Following text deleted: "or within 30 days of last study drug administration"	Section 9.4.2 Serious Adverse Events
It is clarified that pregnancy reporting to the sponsor should be within 6 months (not 84 days) of the last dose of the study drug	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Minor editorial changes	Throughout the protocol

## CLINICAL STUDY PROTOCOL SYNOPSIS

<b>Title</b>	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study in Cat-Allergic Patients with Asthma to Evaluate the Efficacy of a Single Dose of REGN1908-1909 to Reduce Bronchoconstriction Upon Cat Allergen Challenge
<b>Site Location(s)</b>	France
<b>Principal Investigator</b>	Professor Frédéric de Blay
<b>Objective(s)</b>	<p><b>Primary Objective:</b> To evaluate the prophylactic efficacy of REGN1908-1909 (anti- <i>Felis catus</i> [domestic cat] allergen 1 [Fel d 1]) administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat in the prevention of a Controlled Cat Allergen Challenge-induced early asthmatic response (EAR) assessed by measures of lung function (Forced expiratory volume in 1 second: FEV1) compared to placebo-treated patients on day 8.</p> <p><b>Secondary Objectives:</b></p> <p><b>Secondary Efficacy Objectives</b></p> <ul style="list-style-type: none"><li>• To evaluate the prophylactic efficacy of REGN1908-1909 administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat, in the prevention of a Controlled Cat Allergen Challenge-induced:<ul style="list-style-type: none"><li>○ Early asthmatic response (EAR) assessed by measures of lung function (FEV1) compared to placebo-treated patients on days 29, 57, and 85</li><li>○ Allergic rhinitis symptoms assessed by total nasal symptom score (TNSS) compared to placebo patients on days 8, 29, 57, and 85</li><li>○ Ocular symptoms assessed by total ocular symptom score (TOSS) compared to placebo patients on days 8, 29, 57, and 85</li></ul></li><li>• To evaluate the prophylactic efficacy of REGN1908-1909 administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat to increase the exposure to cat allergen, measured as a product of minute ventilation and time, required to induce EAR in a Controlled Cat Allergen Challenge (40 ng/m<sup>3</sup> Fel d 1 allergen x minute ventilation x time) as compared to placebo patients on days 8, 29, 57, and 85</li></ul>

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**Secondary Safety Objective**

To evaluate the safety and tolerability of REGN1908-1909 vs. placebo in patients with cat allergen-triggered asthma.

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**Study Design**

This is a phase 2, randomized, double-blind, parallel-group, single-dose study in approximately 60 cat-allergic patients with mild asthma (Global initiative for asthma stage 1 [GINA stage 1]), who are not living with a cat, to evaluate the efficacy of a single 600 mg SC prophylactic dose of REGN1908-1909 in the prevention of a Controlled Cat Allergen Challenge-induced EAR as assessed by FEV1 and compared to placebo-treated patients.

This single-site study will incorporate specialized safety monitoring appropriate for a design that intends to induce reductions in FEV1 in a population with mild asthma.

The study consists of up to a 12-week screening period followed by 1:1 randomization on day 1 to receive 600 mg REGN1908-1909 or placebo administered SC in eligible patients followed by a 12-week assessment period and a 4-week safety follow-up period. During screening, patients undergo a 2-hour placebo exposure in an environmental exposure unit (EEU), a state-of-the-art windowed ISO 8 cleanroom with 20 seats, located in Nouvel Hôpital Civil in Strasbourg, France. While comfortably seated in the EEU, patients undergo spirometry every 10 minutes using portable spiroometers which convey data in real time to the clinical monitoring room adjacent to the EEU. Patients with nonspecific bronchial hyperreactivity in the placebo EEU exposure, defined as those who experience an FEV1 reduction >10% on 3 consecutive occasions while undergoing spirometry every 10 minutes, will be excluded from continuing in the study. Patients who are not excluded after the placebo exposure will undergo a baseline 2-hour Controlled Cat Allergen Challenge.

During the Cat Allergen Challenge, standardized cat allergen extract (40 ng/m<sup>3</sup>) is continuously nebulized into the EEU and patients perform spirometry every 10 minutes until they experience bronchoconstriction, when their FEV1 is reduced by  $\geq 20\%$ , defined as an EAR. Patients leave the EEU once they achieve an EAR, and they are then monitored outside of the EEU in an observation room for 6 hours. Patients who fail to achieve an EAR within 2 hours in the baseline Cat Allergen Challenge in the EEU will be excluded from the study. During the time they are in the EEU, they record their TNSS, a validated, patient-reported, composite symptom assessment of congestion, itching, rhinorrhea, and sneezing, and TOSS, a validated, patient-reported, composite symptom assessment of ocular symptoms (itching, redness, tearing, and swelling) using handheld tablets every 20 minutes. During the 6-hour observation

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period after leaving the EEU, FEV1 is measured every 30 minutes to assess for a late asthmatic response (LAR), defined as a delayed drop of 15% after exiting the EEU. During the 6-hour observation period, TNSS, TOSS, and chest symptom questions are recorded every hour. At the end of the 6-hour monitoring period, patients are discharged home if FEV1  $\geq$ 90% of the baseline value; if FEV1 is <90% of the baseline value, patients will continue to be monitored at the clinic until the patient meets criteria for discharge. FEV1 is monitored during 6 hours after the EEU session using portable spiroometers, and patients are followed up 18 hours after leaving the clinical unit. Patients meeting eligibility criteria are randomized to a single dose of REGN1908-1909 (600 mg SC) or placebo. Patients then return to the study site to undergo a 4-hour Cat Allergen Challenge in the EEU on days 8, 29, 57, and 85 with a 6-hour observation period, at which time EAR, TNSS, and TOSS are assessed using the same time points that were used at baseline. Exploratory measures are also assessed at baseline and throughout the study, as detailed in the exploratory objectives section.

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<b>Study Duration</b>	The duration of the study for a patient is approximately 16 weeks, excluding the screening period.
<b>End of Study Definition</b>	The end of study for this study is defined as the last visit of the last patient.
<b>Population</b>	
<b>Sample Size:</b>	Approximately 60 patients with GINA 1 asthma sensitized to cat allergen.
<b>Target Population:</b>	Male and female adult patients 18 to 65 years inclusive not living with a cat, with cat allergy, as determined by history and positive skin prick test (SPT) to cat hair extract and positive anti-Fel d 1 and cat hair IgE, and whose asthma with allergic rhinitis (AR) with or without conjunctivitis symptoms are triggered by cat exposure.

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**Treatment(s)**

<b>Study Drug</b>	REGN1908-1909
<b>Dose/Route/Schedule:</b>	Single 600 mg subcutaneous (SC) dose (300 mg of each mAb [REGN1908 and REGN1909])
<b>Placebo</b>	Matching placebo
<b>Route/Schedule:</b>	Subcutaneous

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**Endpoint(s)**

**Primary:** Time to EAR upon Controlled Cat Allergen Challenge in an EEU on day 8

**Secondary:**

- Time to EAR upon Controlled Cat Allergen Challenge in an EEU on days 29, 57, and 85
- AUC of the percent change (%/h) in FEV1 induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- AUC of the percent change (%/h) in patient-assessed nasal symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- AUC of the percent change (%/h) in patient-assessed ocular symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- Change and percent change in cat allergen quantity as experienced by patients during exposure (measured by  $40 \text{ ng/m}^3 \times \text{ minute ventilation} \times \text{ time}$ ) on days 8, 29, 57, and 85
- Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study

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**Procedures and Assessments**

The following procedures and assessments will be performed for the purpose of determining study eligibility, characterizing the baseline population, safety monitoring, or determining efficacy:

- Demographics, medical history
- Screening for human immunodeficiency virus (HIV), screening for hepatitis (HBsAg and hepatitis C antibody), follicle-stimulating hormone (FSH) determination (for postmenopausal women if postmenopausal status is in question), spirometry including FEV1, and electrocardiogram (ECG), screening skin prick test (SPT), placebo challenge in EEU, and Controlled Cat Allergen Challenge in EEU

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Patients who meet all inclusion criteria and none of the exclusion criteria are dosed on Day 1.

- Safety Procedures will include vital signs, physical exams, spirometry, ECG, and laboratory testing
- Efficacy procedures will include spirometry (including FEV1), peak nasal inspiratory flow (PNIF), TNSS, TOSS, and chest symptom questions
- Pharmacokinetic (PK) procedures will include sample collection and assessment of serum concentration of REGN1908-1909
- Anti-drug antibody (ADA) procedures include sample collection for status (positive or negative) and titer
- A genomic DNA sample will be collected for pharmacogenetic analyses
- Biomarker procedures will include:
  - Serum total and allergen-specific IgE levels (cat hair, Fel d 1, Fel d 2, Fel d 4, Fel d 7)
  - Standard SPT with cat hair extract and other common allergens
  - Skin prick test with serial allergen titration with cat allergen
  - Fractional exhaled nitric oxide (FeNO)
  - Nasal brushing for exploratory transcriptome analysis

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**Statistical Plan**

Patients will be randomized (1:1) to receive placebo or REGN1908-1909. The primary endpoint is the time to EAR during the day 8 Controlled Cat Allergen Challenge. If a patient remains in the EEU for the maximum time of 4 hours without experiencing an EAR, their time to EAR will be censored at 4 hours. Censoring implies that the time to EAR is at least 4 hours, but the exact time is unknown. The statistical model will be a Cox's proportional hazards model to compare the hazard ratio of EAR on day 8 in REGN1908-1909-treated patients compared to placebo-treated patients, which allows for the patients' time to EAR during the baseline Cat Allergen Challenge to be adjusted for as a covariate. Under this model, the hazard ratio is directly related to the ratio of median duration of tolerated exposure, where a hazard ratio of 1 implies that the median duration of tolerated exposure in the 2 treatment groups is the same.

With 30 patients per treatment group, an increase in median time to EAR from 58 minutes in the placebo treated patients to 132 minutes in patients treated with REGN1908-1909 (ratio of median duration of tolerated exposure of 2.25 or, equivalently, hazard ratio of 0.44) can

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be detected with 84% power assuming a one-sided type I error of 0.05 and a 13% drop-out rate (8 patients). The ratio of median duration of tolerated exposure of 2.25 is based on the estimated effect size in median duration of tolerated exposure observed in a previously reported Cat Allergen Challenge study. The sample size calculation was performed based on the log-rank test comparing the duration of tolerated exposure of 2 groups with the above-mentioned assumptions. The primary analysis will be conducted on the full analysis set (FAS) population, which consists of randomized patients. Efficacy analyses will also be performed on a secondary population, the per-protocol population, as will be discussed in the Statistical Analysis Plan (SAP).

The time to EAR for each treatment will be examined using Kaplan Meier estimates, with patients being censored at 4 hours if they did not experience an EAR. The median time to EAR for each treatment group and the corresponding 95% confidence intervals will be presented for Controlled Cat Allergen Challenges on days 8, 29, 57, and 85. A formal comparison of time to EAR in the treatment groups at day 8 will be performed using a Cox's proportional hazards model, adjusting for allergen exposure and time to EAR in the baseline Controlled Cat Allergen Challenge. Similar comparisons will be made at days 29, 57, and 85 as secondary analyses.

With 60 cat-allergic patients, the study has adequate power to detect differences in the key secondary endpoint: AUC of percent change in FEV1 from baseline Controlled Cat Allergen Challenge in placebo and REGN1908-1909, based on estimated effect sizes from a previous Cat Allergen Challenge study. Specifically, there is 88% power to detect a difference in the mean AUC of 27% in the placebo-treated patients compared to 15% in REGN1908-1909-treated patients.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR	Allergic rhinitis
ARISg	Pharmacovigilance and clinical safety software system
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CPK	Creatinine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
EAR	Early asthmatic response
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EEU	Environmental exposure unit
EPR	Early phase reaction
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
Fel d 1	<i>Felis catus</i> (domestic cat) allergen 1
FeNO	Fractional exhaled nitric oxide
FDA	Food and Drug Administration
FIH	First in human
GINA	Global initiative for asthma
GCP	Good clinical practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgE	Immunoglobulin E
INS	Intranasal corticosteroids
IRB	Institutional Review Board
kAU/L	Kilo allergy units per liter
LAR	Late asthmatic response

**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
NAC	Nasal allergen challenge
PBMC	Peripheral blood mononuclear cell
PCSV	Potentially clinically significant value
PNIF	Peak nasal inspiratory flow
PK	Pharmacokinetics
POM	Proof of mechanism
PPS	Per protocol analysis set
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SIT	Systemic immunotherapy
SMT	Safety monitoring team
SOC	System organ class
SPT	Skin prick test
SQU	Square units
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
WBC	White blood cell

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## 1. INTRODUCTION

Cat allergens are among the most important indoor allergens and a common cause of Type 1 (IgE-mediated) allergic disease worldwide, affecting 10 to 15% of patients with allergic rhinoconjunctivitis and/or asthma. *Felis catus* (domestic cat) allergen 1 (Fel d 1) in cat hair is produced by the skin and by salivary and lacrimal glands of the cat (Kleine-Tebbe, 1993) (Gronlund, 2010). 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. 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) (Neisler, 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). Therefore, it is difficult to avoid exposure to cat hair allergen in the environment.

Nasal and eye symptoms are the most frequently reported and most bothersome of all cat allergy symptoms. Rhinoconjunctivitis is treated with antihistamines and intranasal corticosteroids (INS), which are only moderately effective for nasal symptoms (Ciprandi, 2011). The best reported treatment effects for antihistamines and INS are 5 to 11% relative reduction of total nasal symptoms compared to placebo (Durham, 2016). Intranasal corticosteroids are considered ineffective for allergic eye symptoms.

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 (Perzanowski, 2016) (Olivieri, 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 (Zuberbier, 2010) (Walker, 2011). 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 (Kundig, 2010) (James, 2011). 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 (Leung, 2010) (Durham, 2012) (Scadding 2017).

REGN1908 and REGN1909 are monoclonal antibodies (mAbs), which bind independently and non-competitively to the Fel d 1 allergen and are being developed as a 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 60–90% of the total allergenic activity in cat dander ([Kleine-Tebbe, 1993](#)).

These fully human, high-affinity IgG4 monoclonal antibodies 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 42% improvement in TNSS (total nasal symptom score) nasal challenge response 8 days after REGN1908-1909 administration, compared with placebo.

This magnitude of effect is approximately 2-fold above what was observed in a natural-exposure, perennial allergic rhinoconjunctivitis study with intranasal corticosteroids ([Wu, 2013](#)). The effect of REGN1908-1909 on a local response to a nasal allergen challenge could also be observed 4 weeks post-dose, with some patients continuing to show improvement 12 weeks post-dose. In addition, REGN1908-1909 was well tolerated, with no anaphylaxis or evidence of systemic hypersensitivity.

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 native 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.

This phase 2 study (R1908-1909-ALG-1703) aims to investigate the prophylactic effect of REGN1908-1909 to reduce bronchoconstriction in cat-allergic patients with mild asthma when exposed to cat allergen in a controlled environmental exposure unit (EEU). Environmental exposure units are enclosed spaces that control temperature, air flow, and humidity, and provide diffuse allergen exposure to simulate natural circumstances. Because EEU provide allergen exposures which are standardized and reproducible, they have been developed for the investigation of mechanisms and treatment of allergies ([Pfaar, 2017](#)). Globally to date, one EEU clinical trial site has been developed and validated to study asthmatic responses to cat allergen exposures, namely Alyatec in Strasbourg, France. Alyatec is an independent, clinical trial unit situated in the Nouvel Hôpital Civil, directed by pulmonologist and allergist Dr. Frédéric De Blay. The EEU is optimally designed to study patients with asthma upon allergen exposure with real-time electronic monitoring of FEV1 using hand-held spiroometers (Medical International Research Spirobank II) and continuous, direct visualization of patients by clinic staff. Additionally, medications to treat asthma, allergy, and anaphylaxis are readily available, and the hospital emergency room is within the same hospital building as Alyatec in case of emergency.

Alyatec has performed a validation study in the EEU, evaluating 20 patients with cat allergy (by history, positive skin prick test, and positive IgE) and mild asthma, defined by the Global Initiative for Asthma stage 1 (GINA 1: asthma symptoms are controlled with short-acting beta agonists as needed, asthma symptoms are rare, there is no night awakening due to asthma, no exacerbations in the last year, and normal FEV1) (Bateman, 2008), as well as 10 patients with GINA 1 asthma and other allergies, but not cat allergy (by history, negative skin prick test to cat, and negative IgE to cat hair, and positive skin prick test and IgE to other allergens, eg, mite, grass, birch, or ash). All 30 patients were exposed continuously to nebulized cat allergen (40 ng/m<sup>3</sup> Fel d 1) in the EEU for a maximum of 2 hours. Patients underwent spirometry with FEV1 testing every 10 minutes during the EEU exposure and were removed from the EEU when they experienced bronchoconstriction, when their FEV1 was reduced by  $\geq 20\%$ , defined as an EAR. Patients were then monitored outside of the EEU for 6 hours to assess if/when a late asthmatic response (LAR) occurred, defined as a delayed drop of 15% after exiting the allergen exposure in the EEU. Fifty percent (50%) of patients achieved an EAR within 2 hours of EEU exposure and of those who achieved an EAR, approximately 50% of those achieved a LAR. The mean reduction in FEV1 during EAR and LAR was -28.1% range (-20.2 to -44.6) and -19.5% range (-14.9 to -23.5) respectively. Patients experienced EARs as early as within 30 minutes of exposure in the EEU to as late as 121 minutes; the mean time to an EAR was 60 minutes and the mean time to a LAR was 180 minutes (Radu, 2018) (Gherasim, 2018). None of the non-cat-allergic asthmatic patients reached EAR and only experienced minimal changes in FEV1 during cat allergen exposure, with a mean change of FEV1 of 2%, suggesting that the cat-allergen exposure unit is highly specific. All patients tolerated the allergen exposure well. Cat-allergic asthmatic patients who experienced an EAR were offered treatment with a short-acting  $\beta$ 2 agonist upon exiting the EEU chamber, and those who experienced a LAR were also treated with a short-acting  $\beta$ 2 agonist, with all patients experiencing a return of FEV1  $\geq 90\%$  baseline after EAR and LAR. None of the 20 cat-allergic patients with asthma required escalation of asthma therapy beyond a short-acting  $\beta$ 2 agonist, demonstrating that the FEV1 changes induced by the allergen exposure in the EEU are reversible and highly responsive to therapy.

The current 2-arm, placebo-controlled, double-blind, single-dose, randomized, parallel-group proof-of-concept (POC) study will enroll approximately 60 cat-allergic patients with allergic rhinitis (AR) with or without conjunctivitis not currently living with a cat who have a history of GINA 1 asthma (1:1 ratio) (Figure 1). The study will explore over a 12-week assessment period whether a single 600 mg SC prophylactic treatment with REGN1908-1909 can prevent an EAR during exposure to cat allergen as measured by spirometry. During the screening period, patients will be exposed to 2 baseline EEU challenges. To exclude asthmatic patients with reductions in FEV1 not attributable to allergen, the first baseline EEU challenge will be a 2-hour placebo challenge where normal saline will be nebulized into the chamber. Patients will perform spirometry every 10 minutes, and those who experience a reduction in FEV1  $>10\%$  at 3 consecutive spirometry measurements will be excluded from the study. A second screening challenge to cat allergen will then be performed to exclude patients who do not experience an EAR with cat allergen exposure. Cat allergen (40 ng/m<sup>3</sup> Fel d 1) will be nebulized into the EEU for a maximum of 2 hours, with the patient performing spirometry every 10 minutes until the patient reaches EAR (FEV1 reduction  $\geq 20\%$ ) or when the patient voluntarily departs the EEU due to clinically significant allergic and/or asthma symptoms. Upon exiting the EEU, patients will receive a short-acting  $\beta$ 2 agonist, have vitals performed, and then be monitored outside of

the EEU for 6 hours for safety follow-up, during which time the LAR is measured if it occurs. During this 6-hour observation period, spirometry will be performed every 30 minutes, and TNSS, TOSS, and chest symptom questions are recorded every hour. At the end of 6-hour monitoring period, patients will be discharged home if their FEV1 is  $\geq 90\%$  of the baseline value; additional monitoring will be performed if the FEV1 is below 90%. A physical examination and vital signs measurement will also be performed prior to leaving the clinical trial unit. FEV1 will be monitored at home using a portable hand-held spirometer for approximately 18 hours after leaving the clinical unit (a total of 24 hours of monitoring from the end of the EEU exposure). Alyatec's investigator(s) will be connected to spirometry data performed by the patients at home. If there is a 30% drop in FEV1, the investigator(s) will receive an alarm by email to inform him/her about the change in spirometry and the patient will be contacted and evaluated by a medical doctor. Patients will also receive contact information that they will be able to contact Investigator(s) 24 hours a day in case of symptoms.

Cat-allergic patients who fail to reach EAR within 2 hours during baseline exposure will be excluded from the study. At time point days 8, 29, 57, and 85 after randomization, patients will be exposed to the EEU for a maximum of 4 hours or until they reach EAR (FEV1 reduction  $\geq 20\%$ ) and then will be monitored outside of the EEU for 6 hours for safety follow-up, during which time the LAR is measured if it occurs. Although the amount of Fel d 1 that is nebulized into the EEU is continuously  $40 \text{ ng}/\text{m}^3$ , the individual exposure increases over time in association with minute ventilation (the volume of air that can be inhaled or exhaled for 1 minute). Therefore, minute ventilation will be measured in each patient at baseline using spirometry, so that the Fel d 1 airborne exposure, as a product of the individual's minute ventilation and time, can be assessed at each Cat Allergen Challenge on days 8, 29, 57, and 85. Minute ventilation will be measured 1 time at baseline while the patient is at rest rather than in real time in the EEU during cat allergen exposure to minimize variability in the measurement.

The primary objective of this study is to assess the time to EAR at day 8 in a Controlled Cat Allergen Challenge in patients receiving a single dose of REGN1908-1909 (600 mg) on day 1 compared to placebo-treated patients. We hypothesize that patients will be able to tolerate cat allergen for a significantly longer amount of time before they experience bronchoconstriction in an EEU, 8 days after receiving a single dose of REGN1908-1909 as compared to placebo. With 30 patients per treatment arm, an increase in median time to EAR from 58 minutes in the placebo-treated patients to 132 minutes in patients treated with REGN1908-1909 is estimated. A median time to EAR of 58 minutes was observed in cat-allergic patients with asthma upon Controlled Cat Allergen Challenge in the Alyatec validation study ([Gherasim, 2018](#)), and the ratio of median duration of tolerated exposure of 2.25 is based on the estimated effect size observed in a previous Cat Allergen Challenge study ([Corren, 2011](#)). The secondary objectives will assess the safety and tolerability of a single dose of REGN1908-1909 (600 mg) in GINA 1 cat-allergic patients and whether GINA 1 cat-allergic asthmatic patients 1) tolerate longer cat allergen exposure times before experiencing bronchoconstriction in an EEU at days 29, 57, and 85 after a single dose of REGN1908-1909 as compared to placebo, 2) experience reduced nasal (TNSS) and ocular (TOSS) symptom scores in an EEU at days 8, 29, 57, and 85 after a single dose of REGN1908-1909 as compared to placebo, and 3) tolerate a higher Fel d 1 exposure over time in the EEU as measured by  $40 \text{ ng}/\text{m}^3$  Fel d 1  $\times$  minute ventilation  $\times$  time. Exploratory objectives will be performed to elucidate inflammatory and immunological pathways that are affected by REGN1908-1909 and will be included in a separate Exploratory Biomarker Report.

Exploratory objectives will assess total and allergen-specific IgE levels (cat hair, Fel d 1, Fel d 2, Fel d 4, Fel d 7) at baseline and on study drug; standard skin prick test with common allergens at baseline to assess poly-allergy; early-phase allergic skin responses as measured by skin prick test with serial allergen titration with cat hair extract at baseline, day 29, and day 85; nasal congestion in an EEU as measured by peak nasal inspiratory flow (PNIF) at the time of EAR and 6 hours after exposure; biochemical measures of asthma control as measured by fractional exhaled nitric oxide (FeNO) at baseline and 24 hours after EEU exposure; patient-reported chest symptoms in an EEU as measured by chest symptom questions every 20 minutes in the EEU and hourly for 6 hours after EAR; and changes in type 2 inflammation in the nasal mucosa as measured by RNA sequencing, measured at baseline and 6 hours after EEU exposure.

## 2. STUDY OBJECTIVES

### 2.1. Primary Objective

To evaluate the prophylactic efficacy of REGN1908-1909 (anti-Fel d 1) administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat in the prevention of a Controlled Cat Allergen Challenge-induced early asthmatic response (EAR) assessed by measures of lung function (FEV1) compared to placebo-treated patients on day 8.

### 2.2. Secondary Objective(s)

#### Secondary Efficacy Objectives

- To evaluate the prophylactic efficacy of REGN1908-1909 administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat, in the prevention of a Controlled Cat Allergen Challenge-induced:
  - Early asthmatic response (EAR) assessed by measures of lung function (FEV1) compared to placebo-treated patients on days 29, 57, and 85
  - Allergic rhinitis symptoms assessed by TNSS compared to placebo patients on days 8, 29, 57, and 85
  - Ocular symptoms assessed by total ocular symptom score (TOSS) compared to placebo patients on days 8, 29, 57, and 85
- To evaluate the prophylactic efficacy of REGN1908-1909 administered as a single dose on day 1 in cat-allergic asthmatic patients not living with a cat to increase the exposure to cat allergen, measured as a product of minute ventilation and time, required to induce EAR in a Controlled Cat Allergen Challenge ( $40 \text{ ng}/\text{m}^3$  Fel d 1 allergen  $\times$  minute ventilation  $\times$  time) as compared to placebo patients on days 8, 29, 57, and 85

**Secondary Safety Objective:** To evaluate the safety and tolerability of REGN1908-1909 vs. placebo in patients with cat allergen-triggered asthma.

## 2.3. Exploratory Objective(s)

### 2.3.1. Exploratory Efficacy Objectives

- To evaluate LAR on days 8, 29, 57, and 85
- To evaluate whether a single prophylactic SC administration of REGN1908-1909 inhibits a wheal-and-flare response to a skin prick test with serial allergen titration with cat allergen in patients with cat allergen-triggered asthma and AR with or without conjunctivitis on days 29 and 85
- To evaluate the prophylactic efficacy of REGN1908-1909 in cat-allergic patients not living with a cat to reduce respiratory symptoms induced by a Controlled Cat Allergen Challenge on days 8, 29, 57, and 85 as measured by chest symptom questions
- To assess the prophylactic effect of REGN1908-1909 on biochemical measures of asthma control (FeNO) in patients with cat allergen-triggered asthma induced by a Controlled Cat Allergen Challenge on days 30 and 86 and measured 24 hours after challenge
- To assess the prophylactic effect of REGN1908-1909 on TNSS, TOSS, and chest symptoms up to 24 hours after leaving the EEU
- To assess the prophylactic effect of REGN1908-1909 on objective measures of nasal congestion (PNIF) in patients with cat allergen-triggered asthma induced by a Cat Allergen Challenge on 8, 29, 57, and 85
- To assess the relationship between baseline cat allergen-specific IgE levels (cat hair sIgE, Fel d 1 sIgE), total IgE, and the ratio of cat allergen-specific IgE/total IgE (cat hair sIgE/total IgE and Fel d 1-specific IgE/total IgE levels) and efficacy of REGN1908-1909
- To assess the relationship between cat allergen-specific IgE levels (Fel d 2, Fel d 4, Fel d 7, and other common allergens) at screening and baseline to evaluate the relationship between response to REGN1908-1909 and poly/mono-sensitization
- To assess the extent of REGN1908-1909 interference with the measurement of endogenous anti-Fel d1 IgE in baseline samples and its relationship to clinical benefit
- To assess the degree to which REGN1908-1909 prevents induction of type 2 inflammation in the nasal mucosa as assessed by RNA sequencing of nasal brushing on day 29.

### **2.3.2. Exploratory Pharmacokinetic Objective**

To characterize the concentration-time profile of REGN1908 and REGN1909 after a single SC dose.

### **2.3.3. Exploratory Immunogenicity Objective**

To assess the incidence of treatment-emergent anti-drug antibodies (ADA) to REGN1908-1909 in patients with cat allergen-triggered asthma and AR with or without conjunctivitis over time.

## **3. HYPOTHESIS AND RATIONALE**

### **3.1. Hypothesis**

A single SC dose of REGN1908-1909 600 mg (anti-Fel d 1) will reduce cat allergen-induced bronchoconstriction, as measured by an increase in time to EAR upon Cat Allergen Challenge in an EEU, in cat-allergic asthmatic patients not living with a cat compared to placebo-treated patients.

### **3.2. Rationale**

#### **3.2.1. Rationale for Study Design**

An EEU that simulates natural exposure and provides standardized and reproducible cat allergen levels will be used to demonstrate the effectiveness of REGN1908-1909. Environmental exposure units have been used for modeling environmental exposure and response to a variety of anti-allergic agents, including antihistamines, anti-leukotrienes, intranasal and inhaled corticosteroids, and immunologics (Wood, 1995) (Perry, 2004) (Corren, 2011) (Patel, 2013). The EEU provides a means of simultaneously exposing upper and lower airways to uniform concentrations and particle sizes of allergen under uniform conditions, including CO<sub>2</sub> levels, humidity, and temperature. The nebulized cat hair extract concentration that will be used in this study is 40 ng/m<sup>3</sup> Fel d 1. Forty (40) ng/m<sup>3</sup> Fel d 1 is the equivalent concentration that patients experience upon live cat exposure in homes where cats live (Blay, 1990) (Custovic, 1998) (Bollinger 1996) (Bollinger 1998). When tested in an EEU, 40 ng/m<sup>3</sup> (but not 20 ng/m<sup>3</sup>) Fel d 1 produced a reduction in FEV1  $\geq 20\%$  in over 50% of cat-allergic GINA 1 asthmatic patients (Gherasim, 2018). In the current study, patients will be exposed to a placebo exposure of saline only in the EEU during screening to exclude patients who have a non-specific reduction in FEV1 upon EEU exposure. Patients who experience a non-specific reduction in FEV1  $> 10\%$  in 3 consecutive spirometry measurements will be excluded from the study (Diamant, 2014). Patients will next undergo a screening EEU exposure to nebulized cat hair extract (40 ng/m<sup>3</sup> Fel d 1). Patients who fail to experience a reduction in FEV1  $\geq 20\%$  within 2 hours in the Cat Allergen Challenge in the EEU will be excluded from the study. FEV1  $\geq 20\%$  is considered to be a clinically significant reduction and this threshold has been used for previous inhaled allergen bronchoprovocation tests (Diamant, 2014) (O'Byrne, 2009).

Patients who live with a cat will not be allowed to enter the study because these persons have a modified immune system with high levels of specific “blocking antibodies” IgG/IgG4 which may ameliorate the IgE-mediated allergic response (Erwin, 2014). Since this type of immune

response might induce clinical tolerance, diminishing the severity of symptoms upon allergen exposure, this study will exclude patients living with cats. Patients with moderate and severe asthma (GINA 2-5) will be excluded from the study, as moderate asthmatic patients are unable to tolerate challenges with cat allergen for longer than 30 minutes ([Corren, 2011](#)).

The follow-up period of 16 weeks (12 weeks of assessment plus 4-week safety follow-up) after the single dose of REGN1908-1909, plus an additional 30 days of follow-up for any SAE that occurs after study completion, represents a follow-up period of approximately 5 months, within the 4 to 5 half-life window for antibody levels to fall to largely undetectable levels. Serious adverse events considered by the investigator to be related to the investigational product are to be reported even if onset is greater than 30 days from the end of study.

### **3.2.2. Environmental Exposure Unit**

Alyatec's EEU is a 65 m<sup>2</sup> International Standards Organization 8 cleanroom (Standard 14644-1) with continuous air circulation, containing 20 seats to accommodate up to 20 patients at 1 time, and with an anteroom and exit room. The EEU contains 10 particle counters spread equally throughout the room, and glass fiber filters adjacent to seats to be used for Fel d 1 allergen testing by ELISA. Standardized, commercially available cat hair extract prepared by a pharmacist is nebulized into the EEU through a specialized system that maintains consistent particle counts and Fel d 1 counts approximating 40 ng/m<sup>3</sup> across the 20 seat positions of the EEU. Particle counts and Fel d 1 counts fall below the limit of detection within minutes of stopping the nebulization and Fel d 1 measurements are below the limit of quantification outside of the EEU (eg, in the observation area and in the rest rooms). Other allergens have been tested in the EEU, observation room, and the rest rooms and are below the limit of quantification (eg, house dust mite, birch), suggesting that there is no cross-contamination of allergens. During each exposure, the patients wear protective suits (TS Plus Microgard 2000) to ensure that no contaminant enters or exits the EEU. The cleaning procedure after each EEU exposure session includes the following: rinsing of the nebulization system, disinfectant of the floor, walls, the armchairs, and of all the small material stored in the EEU (Ecowipes, THX medical). Additionally, air qualification is performed by an independent company (Air Qualif) 4 times a year to test for the absence of bacteria and molds in the EEU.

### **3.2.3. Rationale for Dose Selection**

#### **Dose and Regimen of REGN1908-1909**

A single SC dose of 600 mg REGN1908-1909 is the highest dose previously tested in the first-in-human (FIH) study with cat-sensitized and allergic but otherwise healthy patients. This dose of REGN1908-1909 also appeared to be efficacious, reducing the TNSS in a nasal allergen challenge (NAC) study, a proof-of-mechanism (POM) study in cat-induced AR patients, R1908-1909-ALG-1325. This dose has been well tolerated and may provide effect for up to 12 weeks. The pharmacokinetic (PK) profiles of both REGN1908 and REGN1909 were characterized by linear and dose-proportional kinetics. The terminal half-lives of total REGN1908 and REGN1909 were determined to be approximately 30 ( $\pm 7$ ) and 21 ( $\pm 3$ ) days (Standard Deviation), respectively.

### 3.2.4. Rationale for Endpoints

Inhaled allergen bronchoprovocation tests have been used to study the pathophysiology of asthmatic responses to allergens (Popa, 2001) as well as to study the efficacy of anti-allergy therapeutic interventions. For example, Corren et al. reported that omalizumab, which inhibits the binding of IgE to the high-affinity IgE receptors on the surface of mast cells and basophils, reduced bronchoconstriction, as measured by a reduction in FEV1, in cat-allergic asthmatics in a live Cat Allergen Challenge (Corren, 2011).

To determine the efficacy of REGN1908-1909 to reduce bronchoconstriction in cat-allergic patients with asthma, an inhaled allergen bronchoprovocation test using a cat allergen EEU will be used. FEV1 will be measured by spirometry using portable hand-held devices at baseline and during the Cat Allergen Challenge in the EEU until the patient experiences an FEV1 reduction  $\geq 20\%$  of the baseline measurement or when the patient voluntarily departs the EEU due to clinically significant allergic and/or asthma symptoms. A reduction in FEV1  $\geq 20\%$  is considered to be clinically significant (Popa, 2001) and is achievable in patients with mild asthma (GINA 1). In the Alyatec validation study using the cat allergen EEU model to evaluate bronchoconstriction in GINA 1 mild asthmatics allergic to cat, the mean reduction in FEV1 during early and LAR was -28.1% range (-20.2 to -44.6) and -19.5% range (-14.9 to -23.5) respectively. Patients experienced EARs as early as within 30 minutes of exposure in the EEU to as late as 121 minutes, but the mean time to an EAR was 60 minutes (median of 58 minutes) and the mean time to a LAR was 180 minutes (Gherasim, 2018).

In the current study which will use the cat allergen EEU model, the primary endpoint is to assess the time to EAR during 4 hours of continuous exposure to 40 ng/m<sup>3</sup> of cat allergen in patients receiving 1 dose of REGN1908-1909 compared to placebo at day 8. Secondary endpoints are to assess the time to EAR in the cat allergen EEU at day 29 (week 4), day 57 (week 8), and day 85 (week 12) in patients receiving REGN1908-1909 compared to placebo.

Allergic rhinitis and conjunctivitis symptom scores and chest symptom questions will be measured at baseline, during the Cat Allergen Challenge, and for 24 hours following the challenge. Total nasal symptom score is based on regulatory (FDA and EMA) guidance for assessment of AR. Individual nasal symptoms, including rhinorrhea, nasal congestion, nasal itching, and sneezing are evaluated on a 4-point Likert scale (0, none; 1, mild; 2, moderate; and 3, severe) and combined to give the TNSS with a maximum score of 12. Individual ocular symptoms for itching/burning, redness, swelling/puffiness, and tearing/watery eyes are evaluated on a 4-point Likert scale (0, none; 1, mild; 2, moderate; and 3, severe) and combined to give the TOSS, with a maximum score of 12. Individual chest symptoms for chest tightness/shortness of breath/trouble breathing, wheezing, and coughing are evaluated on a 4-point Likert scale (0, none; 1, mild; 2, moderate; and 3, severe). In the omalizumab Cat Allergen Challenge study, there was a significantly lower decrease in the AUC of the change from pre-challenge values in the chest symptom questions (2.1 per hour vs. 5.6 per hour, p <.0001) and a combined nasal-ocular symptom score (NOSS) (2.5 per hour vs. 5.2 per hour, p <.0002 in patients treated with omalizumab as compared to placebo (Corren, 2011). In an allergen challenge in an EEU, allergic rhinoconjunctivitis symptoms typically peak at 3 hours (Ellis, 2017) (Horak, 2009), therefore patients who experience a reduction in FEV1  $\geq 20\%$  in less than 3 hours may not reach their peak allergy symptom scores. However, symptom scores (TNSS, TOSS, chest symptom questions) will be measured every 20 minutes during the cat allergen exposure in the EEU, every

hour for 6 hours following EAR, and thereafter every 2 hours, except when the patient is sleeping, for up to 18 hours after leaving the clinical unit, to compare patients receiving REGN1908-1909 to placebo.

The skin prick test with serial cat allergen titration assesses the early phase reaction (EPR) at 0-60 min. The early phase reaction is characterized by histamine release and is thought to reflect cutaneous mast cell degranulation upon allergen exposure. In the proof-of-mechanism (POM) study in cat-induced AR patients, R1908-1909-ALG-1325, the percent change from baseline in normalized average wheal diameter AUC of titrated (100-33,000 SQU/mL) cat hair extract skin prick test, read 15 min after administration on study days 29 and 85, was significantly reduced in REGN1908-1909-treated patients as compared to placebo-treated patients ([Orengo, 2018](#)). These data suggest that the skin prick test with serial cat allergen titration can be used to test pharmacodynamics of 1 dose of REGN1908-1909 in this study.

Serum antibodies against total cat hair and Fel d 1 will be measured to assess the levels of clinical sensitization against cat in patients prior to the beginning of treatment. As has been widely shown in SIT studies, clinical sensitization to a specific allergen is associated with decreased allergen-specific IgE over time. Concentrations of allergen-specific Ig subclasses, including IgA, IgG1, and IgG4, also increase concomitantly during clinical desensitization therapy. These protective antibodies are considered to be serum “IgE-blocking factors” ([Shamji, 2012](#)) and contribute to the induction of desensitization.

The sponsor hypothesizes that REGN1908-1909 may reduce the induction of genes and inflammatory pathways associated with type 2 inflammation post-EEU exposure. Existing data in the literature suggest that type 2 inflammation in asthmatic or AR patients could be detected by gene expression analysis of nasal tissue samples, collected either by nasal brushing or nasal curettes. For instance, RNA expression analysis of type 2-associated genes in nasal brushings from 50 asthmatic patients and 50 healthy controls have identified “Th2-high” and “Th2-low” patients differentiated by the expression of 70 genes associated with type 2 pathways, including IL-13, IL-5, and periostin. The analysis also revealed that Th2-high patients were more likely to have atopy, atopic asthma, higher blood eosinophil counts, and rhinitis, compared with Th2-low patients. Nasal IL-13 expression was 3.9-fold higher in asthmatic participants who experienced an asthma exacerbation in the past year ([Poole, 2014](#)). In a study of AR patients treated with prednisone or placebo, nasal challenge with Timothy grass was performed. Eight hours post-NAC, significant increases in eosinophil-related gene-expression were detected in the nasal sampling of placebo-treated patients compared to baseline, but not in prednisone-treated patients ([Leaker, 2017](#)). These data suggest that transcriptome analysis of nasal brushings could be used to assess underlying type 2-driven inflammation.

## 4. STUDY VARIABLES

### 4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, weight, height, etc), disease characteristics including medical history, and medication history for each patient.

### 4.2. Primary and Secondary Endpoints

The primary endpoint in the study is the time to EAR upon Controlled Cat Allergen Challenge in an EEU on day 8.

The secondary endpoints are:

- Time to EAR upon Controlled Cat Allergen Challenge in an EEU on days 29, 57, and 85
- AUC of the percent change (%/h) in FEV1 induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- AUC of the percent change (%/h) in patient-assessed nasal symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- AUC of the percent change (%/h) in patient-assessed ocular symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge on days 8, 29, 57, and 85
- Change and percent change in cat allergen quantity as experienced by patients during exposure (measured by  $40 \text{ ng}/\text{m}^3 \times \text{minute ventilation} \times \text{time}$ ) on days 8, 29, 57, and 85
- Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study

### 4.3. Exploratory Efficacy Variable

- Time to LAR upon Controlled Cat Allergen Challenge after an EEU exposure on days 8, 29, 57, and 85
- AUC of the percent change (%/h) in patient-assessed chest symptom question responses
- Levels of FeNO (measured in parts per billion, which is equivalent to nanoliters per liter) 24 hours after Controlled Cat Allergen Challenge (days 30 and 86)
- Peak nasal inspiratory flow (measured in nasal patency, L/min) measured during the EEU exposure according to [Table 1](#)

#### 4.4. Pharmacokinetic Variables

Pharmacokinetic variables are total concentration of REGN1908 and total concentration of REGN1909 in serum, at the sampling times specified in the visit schedule ([Table 1](#)).

#### 4.5. Immunogenicity Variables

Immunogenicity variables include status, titer, and time-point/visit.

Samples in this study will be collected at the visits specified in [Table 1](#) (Schedule of Events).



#### 4.6. Pharmacodynamic and Other Biomarker Variables

##### Serum Antibodies

- Allergen-specific IgE levels (cat hair, Fel d 1) at screening visit 1 (V1) and baseline.
- Allergen-specific IgE levels (Fel d 2, Fel d 4, Fel d 7, and other common allergens) at screening and baseline to assess sensitization status and to evaluate the relationship between response to REGN1908-1909 and poly/mono-sensitization ([van Ree 1999](#)).
- Allergen-specific IgE levels (cat hair, Fel d 1, Fel d 2, Fel d 4, Fel d 7, and other common allergens on days 8, 29, 57, and 85 using blood samples collected prior to the Controlled Cat Allergen Challenge in the EEU
- Additional subclass of serum antibodies (eg, IgG4 against Fel d 1, 2, 4, 7) may be measured at screening, baseline, and on days 8, 29, 57, and 85 using blood samples collected prior to the allergen challenge



##### Skin Prick Test

Standard SPT with cat hair extract and other common allergens will only be performed at screening visit 1 to assess sensitization status.

##### Skin Prick Test with Serial Allergen Titration

Titrated SPT with Serial Allergen Titration with cat allergen will be performed at screening visit 3, days 29, 85, and 113 to confirm pharmacodynamic effects of REGN1908-1909 on wheal size response (mediated by mast cell degranulation). On days when an allergen challenge is performed, the test will be performed prior to allergen challenge.

##### Gene Expression Analysis of Type 2 Inflammation of Nasal Mucosa by RNAseq

Nasal brushing samples will be collected from the patients before and after the allergen challenge at screening, as well as day 29. RNA will be extracted from these samples for RNA sequencing to evaluate temporal changes in the mucosal transcriptome by comparing pre- and post-exposure to cat allergen. The impact on genes associated with type 2 inflammation will also be assessed. The exploratory nasal brushing analyses will not be reported in the clinical study report.

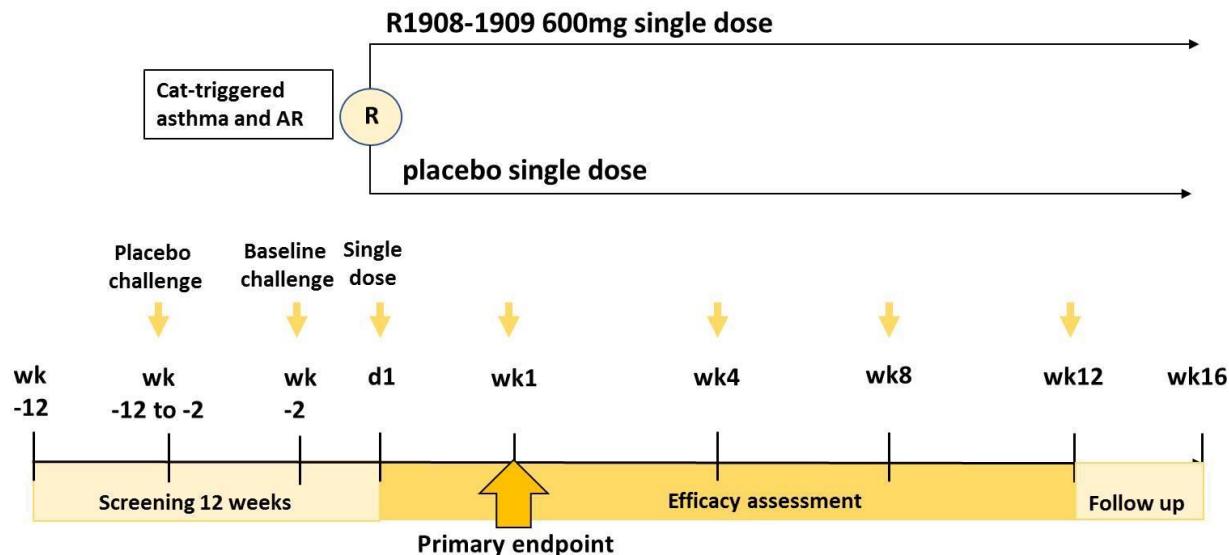
**Interference Assay with REGN1908-1909**

Serum samples collected from patients prior to drug exposure will be tested in an in-vitro competition assay to assess whether REGN1908-1909 effectively inhibits the binding of endogenous anti-fel-d1 IgE to Fel-d1 allergen. Individual blocking efficiencies will be compared to the patient's observed clinical efficacy to determine if efficiency of blocking influences the magnitude of clinical benefit. The analysis will be not reported in the clinical study report.

**5. Study Design****5.1. Study Description and Duration**

This is a phase 2, randomized, double-blind, parallel-group, single-dose study in approximately 60 cat-allergic patients with mild asthma (GINA stage 1) with rhinitis, with or without conjunctivitis to cat hair, who are not living with cats, to evaluate the efficacy of a prophylactic, single 600 mg SC dose of REGN1908-1909 to prevent acute, allergic, lower respiratory symptoms during exposure to cat allergen as measured by spirometry. This single-site study will incorporate clinical monitoring appropriate for conducting a study measuring a mild-to-moderate reduction in FEV1 in the asthmatic population.

The study consists of up to a 12-week screening period followed by 1:1 randomization and treatment of eligible patients with double-blind, single SC dose of study drug at day 1 followed by a 12-week assessment period and then a 4-week safety follow-up period. Patients undergo a saline challenge (placebo challenge) during screening day -85 to -14 where they are exposed to nebulized normal saline for 2 hours in the EEU while FEV1 is monitored every 10 minutes. Patients then undergo an allergen challenge (which involves exposure to cat allergen in the EEU) during screening (baseline challenge) for up to 2 hours, and then allergen challenges on study drug (challenge) at days 8 (week 1), 29 (week 4), 57 (week 8), and 85 (week 12) for up to 4 hours ([Figure 1, Schema 1](#)). A final safety follow-up visit at week 16, 4 weeks after the last Cat Allergen Challenge, will be performed to assess for asthma symptoms after undergoing repeated Cat Allergen Challenges.

**Figure 1: Study Flow Diagram Schema 1**

R: randomization; d: day; wk: week

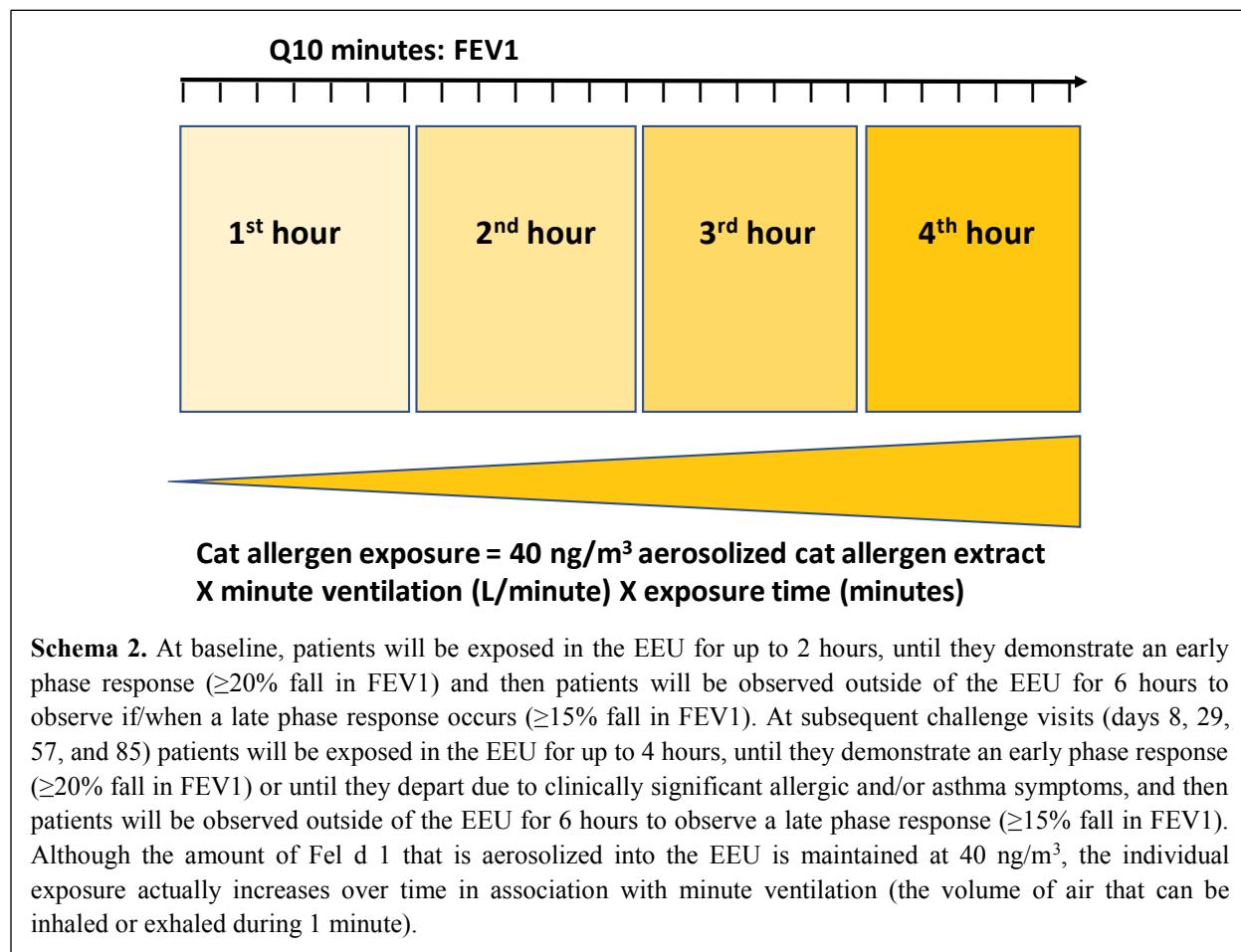
The informed consent will be provided to the patient prior to visit 1 so that he/she has sufficient time to read the informed consent and to ask questions to the investigator.

After obtaining informed consent, patients will be assessed for eligibility during a 3-part screening period ([Table 1](#)).

1. During screening visit 1, patients will undergo eligibility criteria evaluation, collection of medical history, physical examination, vital signs, cat hair extract SPT, standard regional SPT (Dermatophagoides pteronyssinus, Dermatophagoides farinae, dog, aspergillus, Alternaria, birch pollen, 3 grasses pollen, ash pollen), electrocardiogram (ECG), and spirometry. Blood samples will be collected for anti-cat hair and Fel d 1-specific anti-IgE along with other common allergen determination and serum laboratory testing.
2. Eligible patients will undergo a screening placebo challenge in the EEU for up to 2 hours. Patients who experience a  $\geq 10\%$  fall in FEV1 at 3 consecutive spirometry measurements during this placebo challenge will be excluded (eg, over 3 separate consecutive spirometry readings during the 2 hours EEU patients must demonstrate  $\geq 10\%$  fall in FEV1). Baseline skin prick testing with serial allergen titration with cat allergen will be performed at this visit in patients who successfully complete the placebo challenge without experiencing a  $\geq 10\%$  fall in FEV1 at 3 consecutive spirometry measurements.
3. If patients are eligible after the placebo challenge in the EEU, they will undergo a Controlled Cat Allergen Challenge for a maximum of 2 hours. Patients must demonstrate  $\geq 20\%$  fall in FEV1 during exposure and ability to withstand exposure for at least 10 minutes, or they will be excluded. Patients will be removed from the EEU once they have demonstrated  $\geq 20\%$  fall in FEV1, and the time to this reduction in minutes will be recorded. The cat EEU visit 3 during screening must be at least 3 weeks from the cat EEU visit 6 (visits must be spaced apart by at least 3 weeks to avoid allergen priming).

After randomization, patients will undergo serial Controlled Cat Allergen Challenges for a maximum of 4 hours at days 8, 29, 57, and 85 for evaluation of study drug efficacy ([Figure 2, Schema 2](#))

**Figure 2: Study Flow Diagram Schema 2**



Before entry into the cat allergen exposure unit, prohibited medications are withheld (See Prohibited Medications Section [7.8.1](#)), and patients receive a physical examination; chest, nasal, and ocular symptoms, as well as pulmonary function, will be evaluated and recorded. The challenge will not proceed if patients have a TNSS greater than 4, an asthma control test (ACT) score  $< 20$  at any of the screening visits, or FEV1 of less than 70% of predicted value. Patients may leave the exposure unit at any time. Patients wear a disposable suit to protect them from allergen inside the EEU and to avoid contaminating the EEU with other allergens brought in from their clothing, which could interfere with the cat allergen studied.

### Assessments

Study staff-supervised spirometry will be performed in all patients at visits shown in [Table 1](#) with a standard measurement of FEV1 (Section [8.2.2.4](#)).

The asthma control test (ACT), which uses a 5-point Likert scale, will be used prior to the screening cat allergen EEU to determine whether the patient's asthma is well controlled, and again at the final safety follow-up study visit (Section 8.2.2.3).

Patient-reported allergic symptoms (nasal, ocular, and chest symptoms) will be recorded by patients using a 4-point Likert scale (Section 8.2.2.1, Section 8.2.2.2, and Section 8.2.2.3).

Measurement of FeNO, a marker of airway inflammation, will be analyzed from exhaled breath condensates obtained at baseline and 24 hours after the Controlled Cat Allergen Challenges during screening, on day 30 and day 86 (Section 8.2.2.5).

#### **Randomized Single-Dose Treatment/ Follow-up Period (16 weeks):**

Approximately 60 adult patients who meet eligibility criteria will be randomized in a 1:1 ratio into 1 of 2 treatment regimens (n=30 in each group):

- REGN1908-1909 600 mg SC dose at day 1
- Matching placebo SC dose at day 1

All patients will be assessed at scheduled visits for safety, laboratory, and clinical assessments for 16 weeks after the single SC dose of study drug treatment.

The duration of the 16-week follow-up period (12-week assessment period and then a 4-week safety follow up) is based on the time expected for drug levels to be insignificant after the single 600 mg SC dose of REGN1908-1909.

#### **5.1.1. End of Study Definition**

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

#### **5.1.2. Planned Interim Analysis**

No interim analysis is planned.

### **5.2. Study Committees**

#### **5.2.1. Safety Monitoring Team**

A safety monitoring team (SMT) at Regeneron Pharmaceuticals, Inc. will meet periodically to review blinded safety data as needed. The team may be comprised of the medical director, a safety/pharmacovigilance representative, and representatives from biostatistics and data management (BDM), as well as representatives from clinical operations and regulatory affairs. The data to be reviewed includes but is not limited to:

1. Treatment-emergent adverse events that result in an early study withdrawal
2. Serious adverse events (SAEs)
3. Selected laboratory tests, as deemed appropriate by the SMT
4. Additional AEs of interest to the SMT

Appropriate action, if needed, will be taken based upon this review and in consultation with the medical monitor.

### **5.2.2. Independent Data Monitoring Committee**

An IDMC, composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of cumulative unblinded safety data. If requested, the IDMC may have access to any other data for the purposes of a risk-benefit assessment.

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 the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

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

## **6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS**

### **6.1. Number of Patients Planned**

Approximately 60 patients are planned for enrollment.

### **6.2. Study Population**

The population will be adults 18-65 years inclusive of males and females with cat-induced asthma (GINA 1) and AR with or without conjunctivitis symptoms with cat sensitization confirmed at screening.

#### **6.2.1. Inclusion Criteria**

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

1. Generally healthy men and women between the ages of 18 and 65 inclusive at the time of screening.
2. Documented or patient reported history (for at least 2 years) of symptomatic cat allergen-triggered asthma with rhinitis with or without conjunctivitis 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 hair and Fel d 1 (>0.35 kAU/l at screening)
  - c. History of asthma GINA 1
  - d. Screening FEV1  $\geq$ 70% predicted after withholding long-acting  $\beta$ 2-agonists for > 36 hours and short-acting  $\beta$ 2-agonists for > 6 hours
  - e. Demonstrated  $\geq$ 20% fall in FEV1 within 2 hours during Cat Allergen Challenge in EEU and ability to withstand exposure for at least 10 minutes during screening
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide informed consent signed by study patient or legally acceptable representative

5. Patients covered by health social identification number
6. Able to understand and complete study-related questionnaires
7. No cat exposure at home for the past year and must continue having no exposure at home during the study; cat exposure outside of the home shall be avoided for at least 1 week prior to any Cat Allergen Challenge and during the defined follow-up period.
8. Less than 10 pack-years of smoking history

#### **6.2.2. Exclusion Criteria**

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

1. Patients who experience a  $\geq 10\%$  fall in FEV1 at 3 consecutive spirometry measurements during the placebo challenge
2. Positive human immunodeficiency virus (HIV) test
3. Positive hepatitis test (HBsAg and hepatitis C antibody)
4. History of significant multiple and/or severe allergies (including latex gloves) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food
5. Participation in a prior REGN1908-1909 clinical trial
6. History of severe anaphylactic or severe asthmatic reactions to cat exposure
7. Active lung disease other than asthma
8. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to screening
9. Persistent chronic or recurring acute infection requiring treatment with antibiotics, antivirals, or antifungals, or any untreated respiratory infections within 4 weeks prior to screening
10. Serum creatinine, creatinine phosphokinase (CPK), alkaline phosphatase, hepatic enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), total bilirubin (unless the Investigator has evidence that increased indirect bilirubin corresponds to a Gilbert's-type syndrome) that exceed 1.5 x the upper limit of normal (1.5 x ULN), or 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
11. 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 cardiovascular disease, hypertension, diabetes, etc.)
12. Patients taking any prohibited treatment (Section [7.8.1](#) Prohibited Medications)
13. Use of systemic corticosteroids within 8 weeks prior to screening visit 1
14. Use of anti-IgE or other biological therapy within 6 months prior to screening visit 1

15. History of SIT with cat allergen or vaccines against cat allergy within 5 years of screening visit 1
16. SIT with any allergen within 6 months prior to screening visit 1
17. Significant rhinitis, or sinusitis, due to daily contact with other allergens causing symptoms that are expected to coincide with the baseline or the final cat allergen exposure unit assessments as assessed by the investigator, before each exposure
18. Patients who anticipate major changes in allergen exposure in their home or work environments that are expected to coincide with the baseline or the final cat allergen exposure assessments as assessed by the investigator
19. Hospitalization for any reason within 30 days prior to screening visit 1
20. 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
21. Treatment of asthma requiring systemic (oral or parenteral) corticosteroid treatment more than twice within 12 months or once within 3 months prior to screening or has been hospitalized or has attended the ER/Urgent Care facility for asthma more than twice in prior 12 months before screening.
22. History of hypersensitivity to corticosteroids or antihistamines, or drug treatment excipient
23. Known sensitivity to doxycycline, tetracyclines, or to any of the components of the investigational product formulation
24. Positive serum human chorionic gonadotropin pregnancy test at the screening visit or urine pregnancy test at the baseline visit
25. Pregnant or breastfeeding women
26. Women of childbearing potential\* 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 6 months after the last dose of study drug. 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
  - e. and/or sexual abstinence†, ‡.

\*Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential; if in question, a follicle stimulating hormone (FSH) of  $\geq 25$  mU/mL must be documented.

f. Pregnancy testing and contraception are not required for women with documented hysterectomy, bilateral oophorectomy, or tubal ligation.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

‡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. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for 6 months after the last dose of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for 6 months after the last dose of study drug.
28. Inability to understand and act upon the information provided (what to do in an emergency situation, patient has difficulty understanding/communicating, etc)
29. Patient under legal custody, guardianship, or curatorship
30. Screening asthma control test (ACT) <20 at any screening visits

NOTE: Patients may be rescreened after asthma control improves. Patients who are rescheduled must demonstrate stable asthma control by having an ACT  $\geq 20$  at 2 consecutive visits, separated by at least a week.

### **6.3. Premature Withdrawal from the Study**

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

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study. Criteria for withdrawal include but are not limited to the following:

- The patient experiences a FEV1 reduction  $\geq 50\%$  from the baseline measurement of FEV1 (before EEU exposure) at any time during the study
- The patient requires emergency treatment of asthma or of a hypersensitivity reaction in a hospital or emergency room
- The patient experiences a systemic allergic response and/or anaphylaxis requiring epinephrine

The investigator and/or sponsor have the right to withdraw a patient from the study if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

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

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

## **6.4. Replacement of Patients**

Patients prematurely discontinued from study after randomization will not be replaced.

# **7. STUDY TREATMENTS**

## **7.1. Investigational and Reference Treatments**

Pre-lyophilized 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.

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.

Placebo will be supplied in vials that match, but do not contain the protein. Colored, transparent “blinding labels” will be placed on drug product syringes to blind staff that will administer drug products.

This is a single-dose study. Study drug will be administered SC on day 1, by the investigator, or other qualified study personnel. Patients will be randomized in a 1:1 ratio to receive 600 mg REGN1908-1909 or placebo.

Three 2.0 mL SC injections will be administered in the abdomen in different quadrants.

Instructions on dose preparation are provided in the pharmacy manual.

## **7.2. Rescue Treatment(s)**

After each allergen challenge, all patients will leave the site with a rescue treatment kit containing: short-acting  $\beta$ 2 agonist, oral corticosteroids, and oral antihistamines. The patients will also receive oral and written information about the procedure to be followed in case of the occurrence of AEs which may be related to the study, as well as the telephone number of the physicians of the study.

## **7.3. Dose Modification and Study Treatment Discontinuation Rules**

### **7.3.1. Dose Modification**

This is a single-dose study. Dose modification for an individual patient is not allowed.

### **7.3.2. Study Drug Discontinuation**

Study drug discontinuation is not applicable in this single-dose study. Patients who opt out of EEU challenges after receipt of study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule except for EEU exposures and EEU related procedures (see Section 8). Patients who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

#### **7.3.2.1. Reasons for Permanent Discontinuation of Study Drug**

Permanent study drug discontinuation is not applicable in this single-dose study.

### **7.4. Management of Acute Reactions**

Allergen exposure can induce immediate or late allergic reactions in sensitized patients which will be managed as follow:

#### **Allergic Conjunctivitis:**

If there is a conjunctivitis response, topical treatment will be administrated, and oral antihistamines provided as needed at the discretion of the investigator.

#### **Allergic Rhinitis:**

If there is a rhinitis response, topical treatment will be administrated, and oral antihistamines provided as needed at the discretion of the investigator.

#### **Early Asthmatic Response (EAR) and Late Asthmatic Response (LAR)**

During a session in the EEU, an EAR is expected to be mild or moderate. As soon as the patient has a drop in FEV1 of 20% and/or asthma symptoms, the patient will be removed from the EEU and will be treated with short-acting  $\beta$ 2 agonist every 20 minutes for 1 hour if necessary. Patients will stay under supervision in the observation room during 6 hours after leaving the EEU and FEV1 will be monitored every 30 minutes. During this 6-hour monitoring period, a LAR can appear with a drop in FEV1 of 15% and will be treated with short-acting  $\beta$ 2 agonist and corticosteroids if necessary. Approximately at the end of the 6-hour monitoring period, patients will undergo a physical exam and vital signs, including spirometry, and will be discharged home if there are no abnormal findings and if FEV1  $\geq 90\%$  of baseline. If FEV1 is  $< 90\%$  of the baseline value, patients will continue to be monitored at the clinic until the patient meets criteria for discharge. FEV1 will be monitored at home for approximately 18 hours after leaving the clinical unit (a total of 24 hours of monitoring from the end of the EEU exposure). If there is a 30% drop in FEV1 during home monitoring, the investigator(s) will receive an alarm by email to inform about the change in spirometry and the patient will be contacted and evaluated by a medical doctor.

Severe bronchoconstriction will be treated with oxygen, short-acting  $\beta$ 2 agonist by nebulization, and oral systemic corticosteroids.

Under the extremely rare circumstance that patients experience a severe systemic reaction to the EEU (anaphylaxis), with arterial hypotension, angioedema, or urticaria, patients will be treated with adrenaline 0.3 mg IM and will be transferred to the hospital emergency room, which is located within a 5-minute walk of the clinical trial unit.

## 7.5. **Blinding**

Study patients, the principal investigators, and study site personnel (with the exception of the study pharmacist) will be blinded to all randomization assignments throughout the study. The Regeneron Study Director, Medical Monitor, Study Monitor, and all other Regeneron personnel who will be in regular contact with the study site will be blinded to all patient randomization assignments. Study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to blinded individuals involved in study conduct. Although the designated study pharmacist(s)/designee at the study site are unblinded, the treatment assignment will not be provided to site personnel, including the investigator, at any time during the conduct of the study, except in the case of a true emergency.

Selected individuals who are not responsible for the treatment or clinical evaluation of patients may have access to unblinded data as needed for safety review or other data review.

### 7.5.1. **Emergency Unblinding**

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

If unblinding is required:

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

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

## 7.6. **Method of Treatment Assignment**

Approximately 60 patients will be randomized in a 1:1 ratio to receive either 600 mg 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).

## **7.7. Treatment Logistics and Accountability**

### **7.7.1. Packaging, Labeling, and Storage**

A medication numbering system will be used in labeling investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging.

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

### **7.7.2. Supply and Disposition of Treatments**

Study drug will be shipped at a temperature of 2°C to 8°C 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.

### **7.7.3. Treatment Accountability**

All drug accountability records must be kept current.

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

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

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

### **7.7.4. Treatment Compliance**

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

## **7.8. Concomitant Medications**

Any treatment administered from the time of informed consent to the end of the treatment final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study. This excludes all rescue treatment kit medications, taken at home within 24 hours from the EEU exposure. Rescue medications taken from the kit within 24 hours of EEU exposure will be collected separately.

**7.8.1. Prohibited Medications**

1. Use of these concomitant medications within the following time period is preceding any screening visit or any EEU visit:

(NOTE: Patients may be rescheduled 1 time for the screening visit or EEU visit after the time period for taking these concomitant medications has passed.)

- a. Topical or systemic first generation H1 antihistamines (5 days)
- b. Topical or systemic second generation H1 blockers (7 days)
- c. Systemic anti-H2 (8 days)
- d. Atemizole (6 weeks)
- e. Cromoglycates, leukotriene modifiers (7 days)
- f. Systemic steroid treatment (8 weeks prior to screening and during the study)

(NOTE: systemic steroid treatment is allowed if clinically indicated for a LAR treatment after exposure to cat allergen in the EEU.)

- g. Topical steroids (48 hours)
- h. Short-acting  $\beta$ 2 agonists (8 hours)
- i. Long-acting  $\beta$ 2 agonists (eg, salmeterol) (36 hours)
- j. Ultra-long-acting  $\beta$ 2 agonists (eg, indacaterol, vilanterol, olodaterol) (48 hours)
- k. Anticholinergics eg, Ipratropium (Atrovent 40  $\mu$ g) (12 hours)
- l. Long-acting anti-muscarinic agents (7 days)
- m. Methylxanthines (eg, oral theophylline) (24 hours)
- n. Intramuscular corticosteroids (3 months prior to screening and during the study)
- o. Systemic or topical calcineurin inhibitors (14 days prior to screening and during the study)
- p. Tricyclic antidepressants/antipsychotics (14 days)
- q. Topical decongestants (72 hours)
- r. Caffeine-containing drinks or products (8 hours of EEU visits only)

2. History of SIT with cat allergen or vaccines against cat allergy within 5 years of screening
3. SIT with any allergen within 6 months of screening
4. Beta-blockers during the study period
5. Immunomodulatory therapy, anti-IgE, or other biological, agent-based antagonist therapy is not allowed in the 6 months prior to baseline (eg, cyclosporine) or during the study
6. Change in prescription medications within 4 weeks before screening
7. Aspirin and any nonsteroidal anti-inflammatory drug

NOTE: paracetamol is allowed to be used for occasional pain relief.

8. Active treatment for respiratory infections (antiviral, antifungals, or antibiotics) within 4 weeks prior to screening or EEU

### **7.8.2. Permitted Medications**

Use of standard-of-care medications not listed as prohibited will be allowed. Treatment for acute reactions is allowed during the study (See Section [7.4](#)).

## **8. STUDY SCHEDULE OF EVENTS AND PROCEDURES**

### **8.1. Schedule of Events**

Study assessments and procedures are presented by study period and visit in [Table 1](#).

**Table 1: Schedule of Events**

Study Procedure	Screening <sup>1</sup>					Randomization and Treatment Period									End of Study/Early Termination Visit	Unscheduled Visit <sup>24</sup>
	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> V3 <sup>22</sup>	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> V6 <sup>23</sup>	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11			
Visit	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> V3 <sup>22</sup>	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> V6 <sup>23</sup>	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Days	-85 to -14				1	8	9	29	30	57	58	85	86	113		
Window (day)	+7				±3	±2		±2		±3		±3		±3		
Weeks	-12				1	1	2	4	4	8	8	12	12	16		
<b>Screening/Baseline</b>																
Inclusion/Exclusion	X	X	X		X											
Informed Consent	X															
Medical History	X															
Height	X															
Weight	X															
Demographics	X															
HIV screening	X															
Hepatitis screening	X															
Screening Skin prick test for cat hair <sup>4</sup>	X															
Skin prick test for other common allergens <sup>4</sup>	X															
Placebo challenge		X														
Screening Cat Allergen Challenge <sup>3</sup>			X													
Spirometry <sup>5</sup> (includes FEV1)	X	X	X	X	X											

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Study Procedure	Screening <sup>1</sup>					Randomization and Treatment Period									End of Study/Early Termination Visit	Unscheduled Visit <sup>24</sup>
	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Visit	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Days	-85 to -14				1	8	9	29	30	57	58	85	86	113		
Window (day)	+7				±3	±2		±2		±3		±3		±3		
Weeks	-12				1	1	2	4	4	8	8	12	12	16		
Minute ventilation	X															
<b>Treatment</b>																
Randomization <sup>2</sup>					X											
Administer Study Drug <sup>2</sup>					X											
Cat Allergen Challenge <sup>3</sup>						X		X		X		X				
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>Efficacy</b>																
TNSS nasal symptoms score <sup>6</sup>			X	X		X		X	X	X		X	X	X		
TOSS ocular symptoms score <sup>6</sup>			X	X		X		X	X	X		X	X	X		
Chest symptoms questions <sup>6</sup>			X	X		X		X	X	X		X	X	X		
Spirometry (includes FEV1) <sup>5</sup>						X		X	X	X		X	X	X		
PNIF <sup>7</sup>			X			X		X		X		X				
Skin Prick Test with Serial Allergen Titration (Cat-SPT) <sup>8</sup>			X					X				X		X	X	
FeNO <sup>9</sup>		X		X					X				X			

Study Procedure	Screening <sup>1</sup>				Randomization and Treatment Period										End of Study/Early Termination Visit	Unscheduled Visit <sup>24</sup>
	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Visit	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Days	-85 to -14				1	8	9	29	30	57	58	85	86	113		
Window (day)	+7				±3	±2		±2		±3		±3		±3		
Weeks	-12				1	1	2	4	4	8	8	12	12	16		
<b>Safety<sup>10</sup></b>																
Vital Signs	X	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>11</sup>	X <sup>12</sup>		X <sup>12</sup>	X	X <sup>12</sup>		X	X	X	X	
Physical Examination	X		X <sup>27</sup>		X	X <sup>27</sup>		X <sup>27</sup>		X <sup>27</sup>		X <sup>27</sup>		X	X	
Electrocardiogram	X															
ACT	X	X	X											X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Observation			X <sup>20</sup>		X <sup>21</sup>	X <sup>20</sup>		X <sup>20</sup>		X <sup>20</sup>		X <sup>20</sup>				
Distribution of rescue treatment kit			X			X		X		X		X				
Telephone Call <sup>13</sup>						X				X						
<b>Laboratory Testing<sup>14</sup></b>																
Hematology	X				X <sup>15</sup>			X		X		X		X	X	
Blood Chemistry	X				X <sup>15</sup>			X		X		X		X	X	
Urinalysis	X				X			X		X		X		X	X	
βHCG serum pregnancy test	X														X	
Urine pregnancy test (for female patients only) <sup>16</sup>		X	X		X <sup>16</sup>	X		X		X		X		X	X	
FSH test (in postmenopausal	X															

Study Procedure	Screening <sup>1</sup>					Randomization and Treatment Period									End of Study/Early Termination Visit	Unscheduled Visit <sup>24</sup>
	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Visit	V1 <sup>25</sup>	Placebo EEU V2 <sup>25</sup>	Cat EEU <sup>3</sup> , <sup>22</sup> V3	V4	R <sup>2</sup> V5	Cat EEU <sup>22</sup> , <sup>23</sup> V6	Tel .	Cat EEU <sup>22</sup> V7	V8	Cat EEU <sup>22</sup> V9	Tel .	Cat EEU <sup>22</sup> V10	V11	V12		
Days	-85 to -14				1	8	9	29	30	57	58	85	86	113		
Window (day)	+7				±3	±2		±2		±3		±3		±3		
Weeks	-12				1	1	2	4	4	8	8	12	12	16		
women only <sup>28</sup>																
Serum for specific IgE for Fel d 1 and cat hair	X		X		X	X		X		X		X				
Serum for sIgE (Fel-D 2, 4, 7) tests <sup>17</sup>			X		X	X		X		X		X				
Research samples (serum and plasma)			X		X	X		X		X		X		X	X	
Research Samples: whole blood for PBMCs					X	X		X		X		X		X	X	
Nasal brushing samples for RNA analysis <sup>26</sup>			X					X								
Genomic DNA sample <sup>18</sup>				X												
<b>PK<sup>19</sup> and ADA</b>																
Drug conc. sample					X <sup>15</sup>	X <sup>19</sup>		X		X		X		X	X	
ADA sample					X <sup>15</sup>							X		X	X	

**8.1.1. Footnotes for the Schedule of Events Table**

1. All screening-related procedure should be performed between day -85 to -14
2. Randomization/study drug administration (visit 5) must occur within 14 to 28 days of visit 3.
3. Controlled Cat Allergen Challenge is performed as described in the study manual.
4. Screening Skin prick test for cat hair and skin prick testing for other common 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 allergen skin prick testing, blood draw, spirometry, etc).
5. At screening visit 1, a spirometry session will be completed to check for FEV1 inclusion criteria. At visit 2, spirometry will be performed at baseline prior to the placebo EEU challenge, and then every 10 minutes during the placebo challenge, then every 30 minutes in the supervision room for 6 hours. On the Cat Allergen Challenge visits (3, 6, 7, 9, and 10) spirometry will be performed at baseline prior to entry into the EEU, every 10 minutes during the EEU exposure, every 30 minutes in the observation room for 6 hours after leaving the EEU, and then every hour for up to 18 hours after leaving the clinical unit except during sleeping. At visit 5, on the day of randomization, a spirometry session will be performed twice: once prior to receiving the study drug and once prior to leaving the clinical trial unit. Additional spirometry may be performed when prompted by asthma symptoms.
6. TNSS, TOSS, and chest symptom questions are assessed prior to Cat Allergen Challenge, approximately every 20 minutes during the challenge in the exposure unit, every 1 hour for 6 hours post-challenge while patients are being observed in the observation room, and then every 2 hours up to 18 hours after leaving the clinical unit, while they are home, except for the time that they are sleeping. Further details are provided in the study manual.
7. PNIF is assessed prior to Cat Allergen Challenge, approximately at the time of the EAR, and approximately 6 hours post-challenge while patients are being observed in the observation room. Further details are provided in the study manual.
8. Titrated SPT with Serial Allergen Titration with cat allergen will be performed at screening visit 3, days 29, 85, and 113. On days when an allergen challenge is performed, the test will be performed prior to allergen challenge.
9. FeNO is assessed during screening, Visit 4 and then 24 hours after EEU exposure at day 30 and day 86.
10. All safety assessments performed at screening have to be normal and checked against the inclusion/exclusion criteria prior to REGN1908-1909 administration on day 1 (baseline).
11. On day 1, vital signs are taken prior to PK draw, prior to REGN1908-1909 administration, and at 2 hours ( $\pm 10$  min) after completion of the injection.

12. Vital signs are taken prior to entry into the EEU, at exit from the EEU, and prior to leaving the clinical trial unit, and any additional times as needed.
13. Telephone call to collect AEs and concomitant medications, including any medications used from the rescue treatment kit, up to 24 hours after the EEU exposure.
14. Total blood draw at any visit will never exceed 60 mL. Blood volumes are never to exceed 350 mL in 12 weeks.
15. Samples are collected prior to administration of REGN1908-1909.
16. On day 1, urine pregnancy test is completed prior to administration of REGN1908-1909 in women of childbearing potential. Postmenopausal women do not need urine pregnancy testing.
17. Total IgE and allergen-specific serum IgE levels (Fel d 2, Fel d 4, Fel d 7).
18. Genomic analysis is mandatory 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. [REDACTED]
19. PK samples are drawn at any time in the outpatient visit day from day 8 through day 113 (end of study) visit.
20. After exiting the EEU, patients are monitored outside the EEU in an observation room for approximately 6 hours.
21. Patients will be observed for 6 hours in the observation room after receiving a single dose of REGN1908-1909 or placebo.
22. Blood draws should be performed before the EEU exposure
23. Cat EEU visit 3 and visit 6 must be spaced at least 3 weeks apart
24. Assessments and procedures at the unscheduled visit(s) are to be performed at the discretion of the principle investigator.
25. Screening visits 1 and 2 may be combined into 1 visit if the patient has a historical, positive cat SPT or cat IgE that was completed in the last 12 months.
26. Nasal brushing samples will be collected from the patients before and after Cat Allergen Challenge in the EEU on the day of the screening challenge (visit 3) and day 29 (visit 7). Before the challenge in the EEU, a baseline nasal brushing will be performed in 1 nare and the samples will be processed. Six hours from the start of the EEU challenge, a nasal brushing will be performed in the contralateral nare.
27. Physical examination will be performed prior to entering the EEU and approximately 6 hours after the exit or before leaving the observation room, whichever is later.
28. FSH test to be performed in postmenopausal women only, if postmenopausal status in a woman is in question.

ACT: asthma control test; EEU: environmental exposure unit; PBMC: peripheral blood mononuclear cell; R: randomization; V: visit

### **8.1.2. Early Termination Visit**

Patients who are withdrawn from the study after randomization or at any visit before the end of study day 113 will be asked to return to the study site once for an early termination visit consisting of the end of treatment assessments described in [Table 1](#).

### **8.1.3. Unscheduled Visits**

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

## **8.2. Study Procedures**

The following procedures are performed as described in the Study Operations Manual, at time points according to [Table 1](#):

### **8.2.1. Procedures Performed Only at the Screening/Baseline Visit**

The following procedures will be performed to determine study eligibility or to characterize the baseline population: demographics, screening for HIV, screening for hepatitis (HBsAg and hepatitis C antibody), FSH determination (in postmenopausal women if postmenopausal status is in question), medical history, and ECG.

### **8.2.2. Efficacy Procedures**

#### **8.2.2.1. Total Nasal Symptom Score**

Total nasal symptom score is 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 congestion, itching, and rhinorrhea, and from 0 (none) to 3 (5 or more sneezes) for sneezing.

#### **8.2.2.2. Total Ocular Symptom Score**

Total ocular symptom score is from 0 to 12 and is based on a 4-point Likert scale ranging from 0 (none) to 3 (severe) for itching/burning, redness, swelling/puffiness, and tearing/watery eyes.

#### **8.2.2.3. Chest Symptoms Questions**

Individual respiratory symptoms of chest tightness/shortness of breath/trouble breathing, wheezing, and coughing are evaluated on a 4-point Likert scale ranging from 0 (none) to 3 (severe).

#### **8.2.2.4. Spirometry**

Study staff-supervised spirometry will be performed in all patients at visits shown in [Table 1](#) with a standard measurement of FEV1. FEV1 will be measured by means of spirometry at 10-minute intervals during placebo and cat allergen exposures in the EEU, every 30 minutes during the 6-hour observation period after leaving the EEU. Additional spirometry may be performed when prompted by asthma symptoms and/or at the discretion of the investigator.

At home spirometry will be performed hourly for approximately 18 hours after leaving the clinical unit, excluding hours when the patient is sleeping. Additional spirometry may be performed when prompted by asthma symptoms

Spirometry will be measured on the day of randomization prior to receiving the study drug and will be measured after 6 hours prior to leaving the clinic. At the end of the 6-hour monitoring period, patients will undergo a physical exam and vital signs, including spirometry, and will be discharged home if there are no abnormal findings and if  $FEV1 \geq 90\%$  of baseline. Otherwise, in case of  $FEV1 < 90\%$  of the baseline value, patients will continue to be monitored at the clinic until the patient meets criteria for discharge.

Spirometry measurements include FVC (L), FEV1 (L), FEV1/FVC (%), PEF (L/s), FEF 25-75 (L/s). Minute ventilation (L/min) will also be measured using spirometry at screening 1 time while the patient is at rest, and this value will be used to calculate allergen exposure throughout the study (minute ventilation  $\times$  Fel d 1 40 ng/m<sup>3</sup>  $\times$  time).

#### **8.2.2.5. Fractional Exhaled Nitric Oxide**

Fractional exhaled nitric oxide (measured in parts per billion, which is equivalent to nanoliters per liter) will be assessed as described in the study manual at each time point according to [Table 1](#). FeNO is sampled by the nitric oxide analyzer, and the resultant nitric oxide profile versus time or exhaled volume, together with other exhalation variables (eg, airway flow rate and/or pressure), is captured and displayed.

#### **8.2.2.6. Peak Nasal Inspiratory Flow**

Peak nasal inspiratory flow (PNIF) (measured in nasal patency, L/min) will be assessed as described in the Study Operations Manual at each time point according to [Table 1](#). PNIF will be measured and recorded approximately at the time of the EAR during the Cat Allergen Challenge in the EEU and then approximately 6 hours after the EAR during the observational period.

#### **8.2.2.7. Skin Prick Test with Serial Allergen Titration**

The skin prick test (SPT) with serial allergen titration assesses the early phase reaction. Serial dilutions of cat hair extract are placed in duplicate, using skin prick tests on the patient's forearm, and mean wheal diameters are measured 15 minutes after placement.

### **8.2.3. Safety Procedures**

#### **8.2.3.1. Vital Signs**

Vital signs, including temperature, sitting blood pressure, pulse, respiratory rate, and oximetry, will be collected at time points according to [Table 1](#). During EEU visits, vital signs will be collected before each EEU exposure, at the end of the EEU exposure, and 6 hours after the exposure.

### **8.2.3.2. Physical Examination**

A thorough and complete physical examination will be performed at time points according to [Table 1](#). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

### **8.2.3.3. Asthma Control Test**

The asthma control test (ACT) is comprised of patient-reported asthma symptoms using a 5-point Likert scale comprised of 5 elements rated 1-5, with higher scores representing better asthma control. ACT will be performed at screening and at the end of the study at time points according to [Table 1](#).

### **8.2.3.4. Telephone Call**

Patients will be called approximately 24 hours after EEU exposure after the EEU visits on days 8 and 57. Phone calls will collect information on AEs and concomitant medications, including any asthma symptoms and medications used from the rescue treatment kit that the patient was sent home with after the EEU visit. During the call, study staff will recommend any further treatment and visit follow-up if needed based on investigator discretion.

NOTE: patients will return to the Alyatec site approximately 24 hours after the EEU exposure on days 29 and 85 for FeNO measurements, therefore they will not receive a telephone call after these visits per SOE ([Table 1](#)).

### **8.2.3.5. Electrocardiogram**

A standard 12-lead ECG will be performed at screening.

### **8.2.3.6. 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. No greater than the allowed maximum of 350 mL of blood collection will be collected during a 12-week period. Samples for laboratory testing will be collected at visits according to [Table 1](#). Tests will include:

#### **Blood Chemistry**

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)/Urea	Creatine phosphokinase (CPK)
Carbon dioxide	Aspartate aminotransferase (AST)	
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

**Hematology**

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

**Urinalysis**

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

**Other Laboratory Tests**

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 menopausal. Samples will be collected for quantitative assessment of total and 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 medication or its administration, the Medical/Study Director must be consulted.

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

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

**8.2.4. Drug Concentration and Measurements**

Samples for drug concentration will be collected at visits listed in [Table 1](#).

### **8.2.5. Anti-Drug Antibody Measurements and Samples**

Samples for ADA assessment will be collected at time points listed in [Table 1](#).

Detailed instructions for blood sample collection are included in the laboratory manual provided.

### **8.2.6. Pharmacodynamic and Exploratory Biomarker Procedures**

#### **8.2.6.1. Biomarkers**

##### **Serum Antibodies**

Serum allergen-specific IgE levels (cat hair, Fel d 1) will be measured at screening visit 1 and as described in [Table 1](#). Serum allergen-specific IgE levels (Fel d 2, Fel d 4, Fel d 7 and other common allergens) will be measured at baseline and days of EEU challenge to assess sensitization status and to evaluate the relationship between response to REGN1908-1909 and poly/mon-sensitization.

##### **Screening Skin Prick Test**

Standard SPT with cat hair extract and other common allergens will only be performed at screening visit 1 to assess sensitization status.

##### **SPT with Serial Allergen Titration with Cat Hair Extract**

Skin Prick Test with Serial Allergen Titration with cat hair extract (Cat-SPT) will be performed at screening visit 3 and days 29, 85, and end of study to confirm pharmacodynamic effects of REGN1908-1909 on wheal size response (mediated by mast cell degranulation).

##### **Nasal Brushing Samples**

Nasal brushing samples will be collected from the patients before and after Cat Allergen Challenge in the EEU on the day of the screening challenge (Visit 3) and day 29 (Visit 7). Before the challenge in the EEU, a baseline nasal brushing will be performed in 1 nare and the samples will be processed. Six hours from the start of the EEU challenge, a nasal brushing will be performed in the contralateral nare and the sample will be processed. Nasal brushing is performed by a clinician experienced in nasal procedures under direct visualization, by inserting a soft, sterile cytobrush into the nare alongside the inferior nasal turbinate of 1 nostril approximately 0.5 cm above the floor of the nose and 1.5 cm into the nasal cavity and rotating the brush 180 degrees once to the lateral aspect of the nostril. RNA will be extracted from nasal brushing samples and will be used to perform RNA sequencing to determine changes in type 2 inflammation in the nasal mucosa.

##### **Interference Assay with REGN1908-1909**

Serum samples from patients before drug exposure will be tested an in-vitro competition assay to assess whether REGN1908-1909 could inhibit the binding of endogenous anti-fel-d1 IgE to the allergen.

### 8.2.6.2. Environmental Cat Hair Density

The EEU is operated under conditions to maintain stringent control of temperature, relative humidity, ventilation rate, particle number, particle size, and concentration of airborne cat hair extract. Standardized allergen extracts are administered through a nebulizer (SinapTec®) to ensure uniform particle count and size in the EEU. Ten particle counters (APEX R05) positioned in the EEU provide continuous monitoring to confirm uniformity of patient allergen exposure during the allergen challenge. Airborne Fel d 1 concentrations will be sampled at 5 locations in the EEU using 25 mm round fiber filters (Millipore Corp, Bedford, MA) and a multiplex proteomics platform that will be used to measure airborne concentrations of cat allergens. Fel d 1 levels will be measured with a Fel d 1-specific ELISA (King, 2013).

Fel d 1 levels will be measured with a Fel d 1-specific ELISA performed by Indoor Biotechnologies.

### 8.2.7.1. Genomics Study (Mandatory)

DNA samples for the genomics study will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples for DNA extraction should be collected on day 1/baseline (predose) according to **Table 1**. [REDACTED]

## **9. SAFETY DEFINITIONS, REPORTING, AND MONITORING**

### **9.1. Obligations of Investigator**

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

### **9.2. Obligations of Sponsor**

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

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

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

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

### **9.3. Definitions**

#### **9.3.1. Adverse Event**

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

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

### 9.3.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events. See Section [9.4](#) for more information on recording and reporting SAEs.

### 9.3.3. Adverse Events of Special Interest

No AEs of special interest are defined for this study.

## 9.4. Recording and Reporting Adverse Events

### 9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study with the exception of symptoms that occur in response to the EEU within 24 hours following the EEU. Asthmatic and allergic symptoms that occur in response to the EEU are not to be reported as AEs, as they will be recorded as outcome measures. However, AEs that occur in response to allergen exposure in the EEU that are outside of expected symptoms, including events which qualify as SAEs, up to 24 hours after EEU should be reported as AEs and SAEs as applicable.

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

#### **9.4.2. Serious Adverse Events**

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

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

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

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

#### **9.4.3. Other Events that Require Accelerated Reporting to Sponsor**

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

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

**Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 6 months of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria, must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

#### **Adverse Events of Special Interest:**

No Adverse Events of Special Interest (AESIs) have been defined for this study.

#### **9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study**

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

#### **9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results**

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

- the test result is associated with accompanying symptoms,
- the test result requires additional diagnostic testing or medical/surgical intervention,

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

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section [9.5.1](#).

#### **9.4.6. Follow-up**

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

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

### **9.5. Evaluation of Severity and Causality**

#### **9.5.1. Evaluation of Severity**

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

**Mild:** Does not interfere in a significant manner with the patient'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 ER visit or hospitalization; necrosis or exfoliative dermatitis

**9.5.2. Evaluation of Causality****Relationship of Adverse Events to Study Drug:**

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

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

The possible answers are:

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

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

The investigator should justify the causality assessment of each SAE.

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

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

No:

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

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable, temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

**Relationship of Adverse Events to Study Procedure**

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

Is there a reasonable possibility that the AE may have been caused by the EEU exposure?

The possible answers are:

**Not Related:** There is no reasonable possibility that the event may have been caused by the EEU exposure

**Related:** There is a reasonable possibility that the event may have been caused by the EEU exposure

The sponsor will request information to justify the causality assessment of SAEs, as needed.

A list of factors to consider in assessing the relationship of AEs to EEU exposure is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by EEU exposure?

No:

- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the EEU exposure
- do not reappear or worsen when the EEU exposure is resumed
- are not a suspected response to the EEU exposure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable, temporal sequence following the EEU exposure
- resolve or improve after discontinuation of study drug EEU exposure
- reappear or worsen when the EEU exposure is resumed
- are known or suspected to be a response to EEU exposure, based upon preclinical data or prior clinical data

## **9.6. Safety Monitoring**

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

## **9.7. Investigator Alert Notification**

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

## **10. STATISTICAL PLAN**

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

Analysis variables are listed in Section 4.

## 10.1. Statistical Hypothesis

The primary endpoint is the time to EAR upon day 8 Controlled Cat Allergen Challenge in an EEU. During the allergen challenge, the patient may remain in the EEU for a maximum of 4 hours. If a patient does not experience an EAR and remains in the EEU for the maximum time, their time to EAR will be censored at 4 hours. Censoring implies that the time to EAR is at least 4 hours, but the exact time is unknown. The statistical model will be a Cox's proportional hazards model to compare the hazard ratio of EAR on day 8 in REGN1908-1909-treated patients to placebo-treated patients. This model allows for covariate adjustment for allergen exposure and the patient's time to EAR during the baseline Cat Allergen Challenge. Under this model, the hazard ratio is directly related to the ratio of median duration of tolerated exposure, where a hazard ratio of 1 implies that the median duration of tolerated exposure in the 2 treatment groups is the same. The following null and alternative hypotheses of the primary endpoint will be tested:

H0: The hazard rate of EAR during the day 8 Controlled Cat Allergen Challenge is the same in patients receiving REGN1908-1909 and placebo (hazard ratio, HR = 1)

H1: The hazard rate of EAR during the day 8 Controlled Cat Allergen Challenge is lower (ie, the median duration of tolerated exposure is longer) in the REGN1908-1909-treated patients as compared to placebo-treated patients (HR < 1)

## 10.2. Justification of Sample Size

The primary objective of this study is to assess the time to EAR in a Controlled Cat Allergen Challenge in patients receiving REGN1908-1909 compared to placebo-treated patients. Patients will be randomized (1:1) to receive placebo or REGN1908-1909. With 30 patients per treatment arm, an increase in median time to EAR from 58 minutes in the placebo-treated patients to 132 minutes in patients treated with REGN1908-1909 (ratio of median duration of tolerated exposure of 2.25 or, equivalently, hazard ratio of 0.44) can be detected with 84% power assuming a one-sided type I error of 0.05 and a 13% dropout rate (8 patients). A median time to EAR of 58 minutes was observed in untreated patients in the Alyatec validation study ([Gherasim, 2018](#)) and the ratio of median duration of tolerated exposure of 2.25 is based on the estimated effect size observed in a previous Cat Allergen Challenge study ([Corren, 2011](#)). The sample size calculation was performed based on the log-rank test comparing the duration of tolerated exposure of 2 groups with the above-mentioned assumptions.

With 60 cat-allergic patients, this study also has 88% power to detect differences in the key secondary endpoint, AUC of the percent change (%/h) in FEV1 induced by a Controlled Cat Allergen Challenge over the exposure interval (%/h) from baseline to the Controlled Cat Allergen Challenge in patients treated with placebo as compared to REGN1908-1909. This power calculation assumes a mean AUC of 27% in the placebo-treated patients compared to 15% in patients treated with drug, based on a previous Cat Allergen Challenge study and a one-sided type I error of 0.05 ([Corren, 2011](#)). The primary analysis will be conducted on the full analysis set (FAS) population.

## **10.3. Analysis Sets**

### **10.3.1. Efficacy Analysis Sets**

The FAS includes all randomized patients who received any study drug; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of efficacy-related major protocol violations. Final determination of the PPS will be made prior to the database lock and will be outlined in the SAP.

### **10.3.2. Safety Analysis Set**

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF. No missing data will be imputed for safety analyses.

### **10.3.3. Pharmacokinetic Analysis Sets**

The PK population includes all treated patients who received any study drug (safety population) and had at least 1 non-missing blood sample for drug concentration following a single dose of REGN1908-1909. Patients will be analyzed according to the treatment actually received.

### **10.3.4. Anti-Drug Antibody Analysis Sets**

The ADA analysis set will consist of all patients who received any study drug and who had at least 1 non-missing ADA result after a single dose of the study drug. Patients will be analyzed according to the treatment actually received.

## **10.4. Statistical Methods**

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

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

#### **10.4.1. Patient Disposition**

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set (eg, FAS, provided in Section 10.3.2)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

#### **10.4.2. Demography and Baseline Characteristics**

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

#### **10.4.3. Efficacy Analyses**

##### **10.4.3.1. Primary Efficacy Analysis**

The time to EAR will be defined as the time to a  $\geq 20\%$  reduction in FEV1 or when the patient voluntarily departs the EEU due to clinically significant allergic and/or asthma symptoms. The time to EAR for each treatment will be examined using Kaplan Meier estimates with patients being censored at 4 hours if they did not experience an EAR and remained in the EEU for 4 hours. If a patient leaves the EEU before experiencing an EAR and for reasons unrelated to their clinical symptoms, they will be censored at the time of EEU departure. The median time to EAR for each treatment group and the corresponding 95% confidence intervals will be presented for each Controlled Cat Allergen Challenge. A formal comparison of time to EAR in the treatment groups at day 8 will be performed using a Cox proportional hazards model, adjusting for allergen exposure and time to EAR in the baseline Cat Allergen Challenge. The ratio of Fel d 1 IgE to Cat Hair IgE at baseline will also be explored as potential covariate in the model. In patients who receive EEU related medications (including medications given on-site and rescue medications taken at-home), the impact of the carryover of medications between challenges will be explored. A one-sided statistical test of the hazard ratio for placebo compared to drug will be performed.

#### **10.4.3.2. Secondary Efficacy Analysis**

The time to EAR for Cat Allergen Challenges on days 29, 57, and 85 will be evaluated in a similar way to the primary analysis. The time course of asthma response comprising EAR and LAR will be visualized and summarized. Methods for handling missing data in the case that a patient does not complete 1 or more of the Cat Allergen Challenges will be addressed in the SAP.

The AUC of percentage change from baseline FEV1 during the Controlled Cat Allergen Challenge will be analyzed by mixed-effect model repeated measures (MMRM) with the treatment, time, treatment-by-time interaction, and day of challenge as factors and baseline FEV1 as a continuous covariate. An unstructured covariance structure will be utilized; if the model does not converge, an autoregressive structure will be employed. Between-group estimates and nominal p values will be reported for Controlled Cat Allergen Challenges on days 8, 29, 57, and 85. The AUC will be a time-adjusted-based duration of exposure to account for patients exiting the EEU at different times. Missing data from Controlled Cat Allergen Challenges on days 8, 29, 57, or 85 will be accounted for via MMRM. The AUC of percent change in TNSS and TOSS and change and percent change in cat allergen exposure from the baseline Cat Allergen Challenge, will be analyzed in a similar manner.

#### **10.4.3.3. Multiplicity Considerations**

There is no control for multiplicity on the secondary or exploratory endpoints.

#### **10.4.3.4. Timing of Analyses**

##### **10.4.3.4.1. First-Step Analysis**

A first-step analysis may be performed when the last patient completes day 8 of the treatment period and has undergone the Cat Allergen Challenge in the EEU at day 8. No changes in the conduct of the study will be made based on this first-step analysis. The purpose of the first-step analysis is to accelerate the planning of future studies. This will be the final analysis of the primary endpoint of the study. If a decision is made to perform the first-step analysis, in order to maintain study integrity with respect to the treatment follow-up visits, safety visits, and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the first-step analysis and all related activities, restrict other clinical team members and other Sponsor personnel from access to individual patient treatment allocation, and ensure that the dedicated team will not participate in the data review or data decisions for the following treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

#### **10.4.4. Safety Analysis**

Safety analysis will be based on the SAF. This includes reported TEAEs and other safety data (ie, clinical laboratory evaluations and vital sign results). A descriptive summary of safety results will be presented by treatment group.

#### 10.4.4.1. Adverse Events

##### Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the single dose of study drug.
- The treatment period is defined as the time after the single dose of study drug until the end of study (week 16).

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 treatment period.

##### Analysis

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

Summaries of all TEAEs by treatment group will include:

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

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

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

#### 10.4.4.2. 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.

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

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

#### **10.4.4.3. Treatment Exposure**

This is single-dose study.

#### **10.4.4.4. Treatment Compliance**

As a single-dose trial where patients are dosed in clinic, the patients who are randomized but do not receive study treatment drug will be listed.

#### **10.4.5. Pharmacokinetics**

##### **10.4.5.1. Analysis of Drug Concentration Data**

Descriptive statistics of total REGN1908 and total REGN1909 at each sampling time will be provided. Plots of mean concentrations (linear and log scales) versus time will be presented.

##### **10.4.5.2. Analysis of Pharmacokinetic Parameters**

Descriptive statistics of the calculated PK parameter specified in Section [4.4](#) will be provided.

#### **10.4.6. Analysis of Immunogenicity Data**

Formation of ADA will be assessed in individual patients and per treatment group as follows:

- Possible association between changes in PK profile and the presence of R1908-1909 antibodies will be evaluated to assess the potential impact of anti-R1908-1909 antibodies on drug exposure
- Possible association between AEs and the presence of anti-R1908-1909 antibodies may be evaluated to identify a potential impact of anti-R1908-1909 antibodies on safety. Patients with ADA response categories will be listed and summarized as appropriate

#### **10.4.7. Exposure-Response Analysis**

If appropriate, exploratory analyses investigating the relationship between measures of drug exposure and response (including biomarkers) may be performed.

#### **10.5. Interim Analysis**

No formal interim analysis is planned.[10.4.3.4](#)

## 10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

The last assessment before the administration of study drug on day 1 will be considered as the baseline evaluation.

General rules for handling missing data:

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

Visit windows:

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

Unscheduled assessments:

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

## 10.7. 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.

## 10.8. Data Management and Electronic Systems

### 10.8.1. 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 Medidata Rave.

#### **10.8.2. Electronic Systems**

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

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

### **11. STUDY MONITORING**

#### **11.1. Monitoring of Study Sites**

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

The investigator must allow study-related monitoring.

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

#### **11.2. Source Document Requirements**

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

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an 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.

#### **11.3. Case Report Form Requirements**

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF

casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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. 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 which include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, ECs 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.

## **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.

#### **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 EC. A copy of the EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

### **13.2. Patients Confidentiality and Data Protection**

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

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

### **13.3. Ethics Committee**

An appropriately constituted 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 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 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 EC approval letter with a current list of the 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 EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

## **14. PROTOCOL AMENDMENTS**

The sponsor may not implement a change in the design of the protocol or ICF without an EC-approved amendment. All substantial protocol amendments will be approved by the competent authorities before changes are implemented according to national regulations.

## **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 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. STUDY DOCUMENTATION

### 16.1. Certification of Accuracy of Data

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

### 16.2. 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.

## 17. DATA QUALITY ASSURANCE

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

### Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 10.8.1).

### Study Monitoring

The investigator must allow study-related monitoring, EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 11.1, Section 11.2, and Section 12)

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 11.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 11.3 and Section 16.1).

**Study Documentation**

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 11.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 16.2).

**18. CONFIDENTIALITY**

Confidentiality of information is provided as a separate agreement.

**19. FINANCING AND INSURANCE**

Financing and insurance information is provided as a separate agreement.

**20. PUBLICATION POLICY**

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

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**22. INVESTIGATOR'S AGREEMENT**

I have read the attached protocol: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study in Cat-Allergic Patients with Asthma to Evaluate the Efficacy of a Single Dose of REGN1908-1909 to Reduce Bronchoconstriction Upon Cat Allergen Challenge 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 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.

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(Signature of Investigator)

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(Date)

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(Printed Name)

**SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS****(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)***To the best of my knowledge, this report accurately describes the conduct of the study.*

Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study in Cat-Allergic Patients with Asthma to Evaluate the Efficacy of a Single Dose of REGN1908-1909 to Reduce Bronchoconstriction Upon Cat Allergen Challenge

Patient

Protocol Number: R1908-1909-ALG-1703

Protocol Version R1908-1909-ALG-1703 Amendment 2

*See appended electronic signature page*

Sponsor's Responsible Medical/Study Director

*See appended electronic signature page*

Sponsor's Responsible Regulatory Liaison

*See appended electronic signature page*

Sponsor's Responsible Clinical Study Team Lead

*See appended electronic signature page*

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00076626 v1.0

ESig Approval

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