REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol 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
Protocol Number:	R1908-1909-ALG-1703
Clinical Phase:	Phase 2a
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Version/Date:	Statistical Analysis Plan Version 2 / 30 January 2020

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR	Allergic rhinitis
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BUN	Blood urea nitrogen
CPK	Creatinine phosphokinase
EAR	Early asthmatic response
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	*Felis catus* (domestic cat) allergen 1
FeNO	Fractional exhaled nitric oxide
GINA	Global initiative for asthma
GCP	Good clinical practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
INS	Intranasal corticosteroids
kAU/L	Kilo allergy units per liter
LAR	Late asthmatic response
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
PCSV	Potentially clinically significant value
PNIF	Peak nasal inspiratory flow
PK	Pharmacokinetics
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
SOC	System organ class
SPT	Skin prick test
TEAE	Treatment-emergent adverse event
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for the R1908-1909-ALG-1703 study.

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

1.1. Background/Rationale

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).

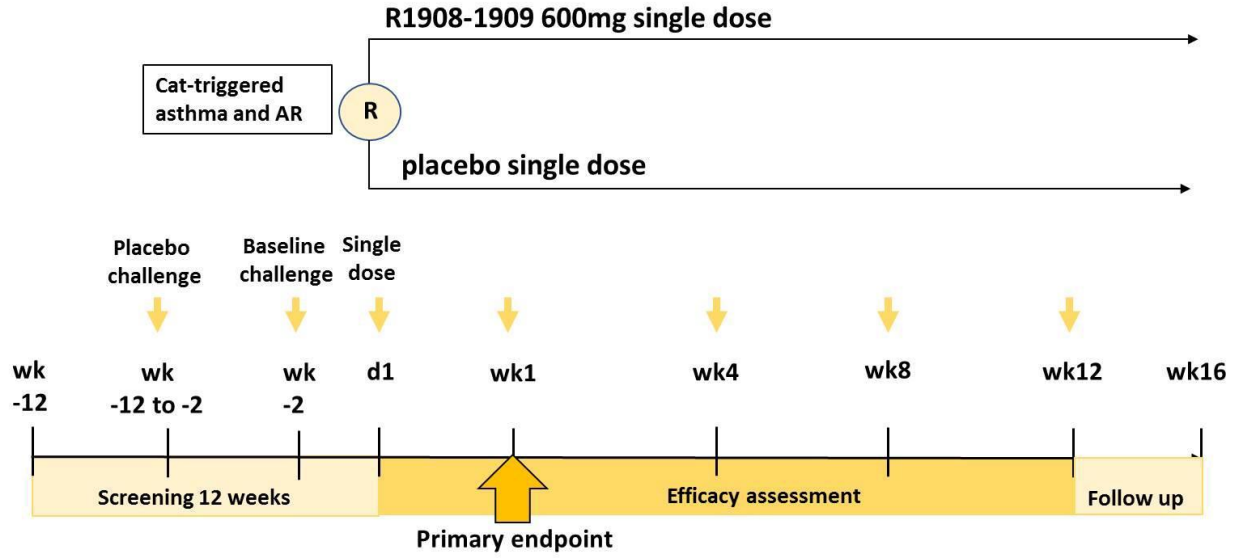
This phase 2 study (R1908-1909-ALG-1703) aims to investigate the prophylactic effect of REGN1908-1909 (anti-Fel d 1) to reduce bronchoconstriction in cat-allergic patients with mild asthma when exposed to cat allergen in a controlled environmental exposure unit (EEU). Environmental exposure units are enclosed spaces that control temperature, air flow, and humidity, and provide diffuse allergen exposure to simulate natural circumstances. Because EEUs 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 spirometers (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.

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. Patients will be randomized (1:1 ratio) to receive REGN1908-1909 or placebo. The study will explore whether a single dose of 600 mg REGN1908-1909 SC can prevent an Early Asthmatic Response (EAR) during exposure to cat allergen as measured by spirometry over a 12-week assessment period. During the screening period, patients will be exposed to 2 EEU challenges. The first EEU challenge will be a 2-hour placebo challenge where normal saline will be nebulized into the chamber to exclude asthmatic patients with reductions in FEV1 not attributable to allergen. 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, the baseline challenge, will then be

performed to exclude patients who do not experience an EAR with cat allergen exposure. Cat allergen (approximately 40 ng/m^3 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 ≥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 β2 agonist, have vitals evaluated, and monitored outside of the EEU for 6 hours for safety follow-up and surveillance for a Late Asthmatic Response (LAR). 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 ≥90% of the baseline value; additional monitoring will be performed if the FEV1 is below 90%. A physical examination will also be performed and vital signs evaluated prior to leaving the clinical trial unit. After leaving the clinical trial unit, spirometry will be performed every hour at home during waking hours using a portable hand-held spirometer for approximately 18 hours (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.

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 ≥20%) and then monitored outside of the EEU for 6 hours for safety follow-up, and surveillance of a LAR. Although the amount of cat allergen that is nebulized into the EEU is continuously 40 ng/m^3 Fel d 1 (approximately), 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 cat allergen 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.

Figure 1: Study Flow Diagram Schema 1



1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of this study is 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.

1.2.2. Secondary Objectives

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 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 (Feld 1 allergen concentration (ng/ m^3)x minute ventilation x 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.

1.2.3. Modifications from SAP Version 1

The following modifications have been made from Version 1 of the SAP as a result of blinded review of the data prior to the first-step analysis:

- Limited biomarker variables and analysis methods have been incorporated.
- The wording in the secondary endpoints for the AUC of TNSS and TOSS have been updated; however, the corresponding objectives will remain the same. In blinded review of baseline data, it was noted that some patients were asymptomatic at baseline. Therefore, the percent change as originally proposed in the SAP cannot be utilized and these endpoints will use a change from baseline metric.
- Analysis methods for exploratory efficacy endpoints have been added.
- The calculation of the cat allergen quantity as experienced by the patient will use the recorded levels of Fel d 1 in the EEU, rather than the target level of 40 ng/m^3.
- The PK and ADA sections have been updated.
- Additional clarifications and details added throughout.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 2, randomized, double-blind, parallel-group, single-dose study in approximately 60 cat-allergic patients (not living with a cat) with mild asthma (GINA stage 1) with rhinitis, with or without conjunctivitis to cat allergen, to evaluate the efficacy of a single 600 mg SC prophylactic 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.

2.2. Sample Size and Power Considerations

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 of Omalizumab observed in a previous Cat Allergen Challenge study performed in a live cat room (Corren, 2011). These estimates of drug effect from this live cat room challenge provide the closest data available for powering this study, as an interventional study has not previously been performed in an EEU with cat allergen. 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, percent change in the AUC of FEV1 induced by a Controlled Cat Allergen Challenge over the exposure interval 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 (Section 3.1).

2.3. Study Plan

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.

The Study event table is presented in Section 10.2.

3. ANALYSIS POPULATIONS

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

3.1. The Full Analysis Set (FAS)

FAS includes all randomized subjects who receive any investigational product and have completed the Day 8 Cat Allergen Challenge. Efficacy analyses will be based on the treatment allocated by the IVRS at randomization (as randomized).

FAS is the primary analysis set for efficacy endpoints.

3.2. The Per Protocol Set (PPS)

PPS includes all subjects in the FAS except for those who may relate to efficacy analysis and who are excluded because of major protocol violations . A major protocol violation is one that may affect the interpretation of study efficacy results. Final determinations of the PPS will be made before data base lock.

Major protocol violation:

The criteria of major protocol deviation are defined as following:

- Had not received study treatment
- Had any major violations of entry criteria
- Had not received treatment as randomized
- Had taken any prohibited medication during the double-blind phase

3.3. The Safety Analysis Set (SAF)

SAF includes all subjects who receive any investigational product and be analyzed 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.

3.4. The Pharmacokinetic Analysis Set (PKAS)

The PKAS includes all treated patients who received any study drug 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.

3.5. The Anti-Drug Antibody (ADA) Analysis Set

The anti-drug antibody (ADA) analysis set will consist of all patients who received any study drug and who had at least 1 non-missing ADA result in the anti-REGN1908 or anti-REGN1909

assay after a single dose of the study drug. Patients will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (year)
- Age range if needed
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) calculated from weight and height (kg/m^2)

The following baseline characteristics will be summarized:

- Minute ventilation (L/min)
- FEV1 (L)
- Baseline challenge FEV1 AUC
- Baseline challenge TNSS AUC
- Baseline challenge TOSS AUC
- Screening skin prick test for cat allergen (mm)
- Skin prick test for other common allergens (mm)
- Skin Prick Test with Serial Allergen Titration, measured by AUC of the wheal sizes (diameter) over log-transformed allergen concentrations
- Baseline serum total IgE
- Baseline serum cat hair sIgE
- Baseline serum Fel d 1 sIgE
- Baseline serum Fel d 2 sIgE
- Baseline serum Fel d 4 sIgE
- Baseline serum Fel d 7 sIgE

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. This includes medications that were started before the study and are ongoing during the study.

Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug.

Concomitant medications/procedures: medications taken or procedures performed following the dose of study drug through the EOS visit, with the exception of rescue treatment kit medications taken at home within 24 hours from the EEU exposure.

4.4. Rescue Medication/or Prohibited Medication During Study

The use of the following concomitant medications is not permitted during the study:

1. Use of these concomitant medications within the following time period 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. Astemizole (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 β2 agonists (8 hours)
   i. Long-acting β2 agonists (eg, salmeterol) (36 hours)
   j. Ultra-long-acting β2 agonists (eg, indacaterol, vilanterol, olodaterol) (48 hours)
   k. Anticholinergics eg, Ipratropium (Atrovent 40 μg) (12 hours)
   l. Long-acting anti-muscarinic agents (7 days)
   m. Methylxanthynes (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 systemic immunotherapy (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 (eg, cyclosporine) is not allowed in the 6 months prior to baseline 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

4.4.1. Rescue Medications

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 β2 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 β2 agonist and corticosteroids if necessary.

After each allergen challenge, all patients will leave the site with a rescue treatment kit containing: short-acting β2 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.

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variables

The primary endpoint in the study is the time to EAR upon Controlled Cat Allergen Challenge in an EEU on day 8. The time to EAR will be defined as the time to a ≥20% reduction in FEV1 or when the patient voluntarily departs the EEU due to clinically significant allergic and/or asthma symptoms. During the allergen challenges (post-randomization), 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.

4.5.2. Secondary Efficacy Variable(s)

The secondary endpoints are:

- Time to EAR upon Controlled Cat Allergen Challenge in an EEU on days 29, 57, and 85

- Change and percent change in AUC of the FEV1 during a Controlled Cat Allergen Challenge over the exposure interval (maximum of 4 hours) from the baseline Controlled Cat Allergen Challenge to challenges on days 8, 29, 57, and 85
- Change in AUC of patient-assessed nasal symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (maximum of 4 hours) from the baseline Controlled Cat Allergen Challenge to challenges on days 8, 29, 57, and 85
- Change in AUC of patient-assessed ocular symptoms induced by a Controlled Cat Allergen Challenge over the exposure interval (maximum of 4 hours) from the baseline Controlled Cat Allergen Challenge to challenges on days 8, 29, 57, and 85
- Change and percent change in cat allergen quantity as experienced by patients during exposure (measured by Fel d 1 allergen concentration (ng/m^3) x minute ventilation x time in hours) from the baseline Controlled Cat Allergen Challenge to challenges on days 8, 29, 57, and 85
- Incidence rates of treatment-emergent adverse events (TEAEs) and serious TEAEs through end of study

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.

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.

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. In the case where a patient has multiple spirometry efforts from the same time point, the study staff will select an effort for use in analysis based on the quality of the efforts as assessed by a flow volume loop.

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 ≥90% of baseline. Otherwise, in case of FEV1 is <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 x Fel d 1 allergen concentration (ng/m^3) x time (in hours)).

4.5.3. Exploratory Efficacy Variables

The exploratory efficacy variables are:

- Time to Late Asthmatic Response (LAR) on days 8, 29, 57, and 85
- Time to Any Asthmatic Response on days 8, 29, 57, and 85
- Change and percent change from FeNO (parts per billion) (adjusted for the pre-challenge baseline) from baseline to days 30 and 86
- Change and percent change in the skin prick test with serial allergen titration, measured by AUC of the wheal sizes (diameter) over log-transformed allergen concentrations with cat allergen from baseline to day 29, 85, and 113

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study 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.

All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the Version 10 or the latest current available version).

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

Acute administration reactions are defined as any AE that occurs during the study drug administration or within 2 hours after the administration is completed. Infusion reactions must be reported as AEs and graded according to the NCI-CTCAE version 4.03 grading scale. Injection site reactions must be reported as AEs and graded according to the Food and Drug Administration (FDA) September 2007 Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

The severity of AEs that are not infusion reactions, or are not covered in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, will be graded according to the following scale:

- Mild: Does not interfere in a significant manner with the subject'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 subject.
- 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 subject's health. Treatment for symptom may be given and/or subject hospitalized.

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

The relationship of AEs to the EEU exposure will be assessed by the blinded investigator.

4.6.2. Adverse Events of Special Interest

No AEs of special interest are defined for this study.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and other.

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Liver function including ALT, AST, alkaline phosphatase, gamma GT, total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin),
- Renal function including creatinine, uric acid,
- Electrolytes including sodium, potassium,
- Metabolic parameters including total proteins, albumin,
- White blood cells (WBCs) including WBCs count and differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes),F
- Red blood cells and platelets including red blood cells count, hemoglobin, hematocrit and platelets count,
- Other

4.6.4. 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.

4.6.5. 12-Lead Electrocardiography (ECG)

12-Lead ECG parameters include

P-R interval ,QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate and etc..

QTcF and QTcB:

$QTcF\ (ms) = QT/RR^{1/3}$ and $QTcB\ (ms) = QT/RR^{1/2}$,

Where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minutes.

4.6.6. Physical Examination Variables

A full or brief physical examination will be performed according to the site's procedures at the time points in Table 1. The limited physical examination will include assessment of HEENT, respiratory, cardiovascular, dermatologic, and allergic/immunologic. The physical examination variable values will be indicated to be either normal or abnormal, clinically significant.

4.7. Pharmacokinetic Variables

Pharmacokinetic variables are total concentration of REGN1908, total concentration of REGN1909 and total antibody (REGN1908+REGN1909) in serum, at the sampling times specified in Section 10.2 (Appendix).

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer and time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Section 10.2 (Appendix).

[redacted]

4.9. Biomarker Variables

- 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) 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).

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for the FAS. A listing of demographics and baseline characteristics will also be presented.

5.2. Medical History

Medical history will be based on the safety population.

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

5.3. Prior/Concomitant Illnesses and Medications

Prior/concomitant illnesses and medications will be based on the safety population.

The number and proportion of patients taking prior/concomitant medications, and prohibited medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4, based on the overall incidence for the combined treatment groups. Patients will be counted only once for each medication class (ATC level 2 and 4) linked to the medication.

Concomitant treatments for asthma and allergic symptoms, including allowed and rescue treatments, will be analyzed similarly.

Concomitant medications used to treat EEU related events will be tabulated separately.

Listings of prior and concomitant medications will be provided.

5.4. Rescue/ Prohibited Medications

Rescue and prohibited medications will be based on both the efficacy and safety population.

The number and proportion of patients taking rescue medications at EEU exit, during the 6-hour observation period on-site and during the at-home monitoring period will be summarized for each treatment group and by type of rescue medication. The total dose of each rescue medication taken per patient will be calculated at each visit at EEU exit, during the 6-hour observation period on-site and during the at-home monitoring period, and will be summarized for each treatment group.

5.5. Subject Disposition

The following summaries will be provided:

Summary of total screened subjects, numbers of FAS, PPS and SAF by treatment and total. Summaries of discontinuations and/or dropouts by reasons and treatments will be presented.

If necessary, the discontinuations and/or dropouts will be compared among the treatment groups. If necessary, the mechanisms, (missing completely at random, missing at random, and non-ignorable) of the missing and/or dropouts will be explored.

5.6. Analyses of Efficacy Variables

The primary endpoint is the time to EAR upon day 8 Controlled Cat Allergen Challenge in an EEU. The time to EAR will be defined as the time to a ≥ 20% reduction in FEV1 (adjudicated by the blinded investigators) or when the patient voluntarily departs the EEU due to clinically significant allergic and/or asthma symptoms. During the post-randomization allergen challenges, 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 cause-specific 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 concentration in the EEU on day 8 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 in the current challenge test on day 8, 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)

5.6.1. Analysis of Primary Efficacy Variable(s)

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 concentration in the EEU and time to EAR in the baseline Cat Allergen Challenge. 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 by including taking medication or not as baseline variable for the model of each subsequent visit. A one-sided 5% statistical test of the hazard ratio for placebo compared to drug will be performed.

If the Cox proportional hazards model does not converge, an extension of the Wilcoxon Rank Sum test comparing the ranks of time to EAR under censoring, adjusted by the covariates specified above, will be used (LaVange and Koch, 2006). As an additional sensitivity analysis, the presence or absence of an EAR within the 4-hour period in the REGN1908-1909 treatment group as compared to placebo will be tested using a Fisher's Exact Test.

Subgroup analyses may be performed by gender, age, baseline IgE and the ratio of Fel d 1 IgE to Cat Allergen IgE at baseline. The ratio of Fel d 1 IgE to Cat Allergen IgE at baseline (log transformed if the distribution is skewed) will also be explored as potential covariate in the Cox proportional hazards model.

5.6.2. Analysis of Secondary Efficacy Variables

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 change and percent change from the Baseline Controlled Cat Allergen Challenge in AUC of FEV1 (L) during the Controlled Cat Allergen exposure will be calculated and analyzed by mixed-effect model repeated measures (MMRM) with the treatment, visit, and treatment-by-visit interaction as factors and the AUC of FEV1 during the baseline Controlled Cat Allergen Challenge, time to EAR during the baseline controlled cat allergen challenge, and allergen concentration in the EEU for each visit as continuous covariates. The primary method for the calculation of the AUC is described in Section 6.2, where last observation carried forward (LOCF) is used to calculate the AUC from 0 to 2 hours. 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. Missing data from Controlled Cat Allergen Challenges on days 8, 29, 57, or 85 will be accounted for via MMRM. The change from the Baseline Challenge in AUC of TNSS and TOSS will be analyzed in a similar manner.

The change and percent change in cat allergen quantity (tolerated exposure) from the baseline Cat Allergen Challenge, will also be analyzed using a similar MMRM model with the treatment, visit, and treatment by-visit interaction as factors and the cat allergen quantity tolerated in the baseline Controlled Cat Allergen Challenge as a covariate.

As a sensitivity analysis the AUC for each endpoint will also be calculated during the period of time where the patient was in the EEU (adjusted for the exposure interval) to give the average value of FEV1, TNSS, and TOSS during the EEU exposure. An MMRM model will be used to model the change (and percent change for FEV1) from the Baseline Challenge in the average value during the EEU exposure. An additional sensitivity analysis will be performed, where the AUC will also be calculated from 0 to 4 hours with LOCF at post-randomization Cat Allergen Challenges following the method outlined in Section 6.2. An MMRM model will be used to model the AUC at each visit (rather than the change in AUC), adjusting for the Baseline Challenge AUC in addition to the time to EAR in the baseline challenge test and the allergen concentration in the EEU. A similar analysis looking at the AUC from 0 to 2 hours with LOCF will also be performed, modeling the raw AUC values at each visit rather than the percent change from baseline.

Subgroup analyses will be performed for the change in AUC of TNSS and TOSS for patients who had a non-zero baseline AUC value and in patients who attained a TNSS of at least 3 during the EEU challenge at baseline.

5.6.3. Analysis of Other Efficacy Variables

The time to LAR at each of the Controlled Cat Allergen Challenges in an EEU will also be explored. After the allergen challenge (when the patient exits the EEU), the patient is observed

onsite for 6 hours and then for an additional 18 hours at home. If a patient does not experience an LAR within the 24-hour period, their time to LAR will be censored at 24 hours.

The time to LAR will be defined as the time to a ≥15% reduction in FEV1 during the 6-hour onsite observation period (adjudicated by the blinded investigators). During the at-home monitoring period up to 24 hours after the patient exits the EEU, the time to LAR will be defined as the time to a ≥15% reduction in FEV1 (confirmed by two spirometry efforts within 5 minutes) along with either rescue medication use (any medication at any dose) within 1 hour or the presence of chest symptoms within 1 hour of the drop in FEV1 (adjudicated by the blinded investigators). Chest symptoms are identified by a response of Mild, Moderate or Severe to the chest symptom questions involving chest tightness, wheezing, cough, throat tightness, and difficulty breathing. Multiple asthma exacerbations during the observation period or at-home monitoring period within the same patient may be adjudicated by the site to be an extended LAR (no more than one LAR within 24 hours of leaving the EEU may be adjudicated, e.g. a subject cannot have more than one LAR within 24 hours of leaving the EEU).

The time to LAR for each treatment will be examined using Kaplan Meier estimates with patients being censored at 24 hours if they did not experience an LAR. The median time to LAR 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 LAR in the treatment groups at each EEU challenge visit will be performed using a Cox proportional hazards model, adjusting for allergen concentration in the EEU. The Kaplan Meier and Cox Proportional Hazards models will be fit separately on the subgroup of patients who receive rescue medications upon EEU exit and for patients who do not. 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 by including taking medication or not as baseline variable for the model of each subsequent visits. A one-sided statistical test of the hazard ratio for placebo compared to drug will be performed.

The ratio of Fel d 1 IgE to Cat Allergen IgE at baseline will also be explored as potential covariate in the Cox Proportional Hazards model and will be log transformed if necessary.

If the Cox proportional hazards model does not converge, an extended Wilcoxon Rank Sum test comparing the ranks of time to LAR, adjusted by the covariates specified above, will be used (LaVange and Koch, 2006).

A time-to-event analysis with competing risks may also be used to examine the incidence of LAR, where the use of rescue medications upon EEU exit is treated as a competing risk with allergen concentration as a covariate in the model. The comparison of LAR-specific and rescue medication-specific cumulative incidences within 24 hours of an EEU challenge across treatment groups will be performed using Gray's method. The model will be fit for each EEU Challenge visit.

As an additional sensitivity analysis, the presence or absence of an LAR within the 24-hour period in the REGN1908-1909 treatment group as compared to placebo will be tested using a Fisher's Exact Test.

The time course of asthma response comprising both EAR and LAR will also be visualized and summarized. A similar analysis will be repeated for the time to any Asthma Reaction. The first asthma reaction that occurs, whether it occurs while the patient is in the EEU, in the on-site 6-

hour observation period, or in the at-home monitoring period, will be treated as the event time. If the subject experiences no asthmatic reaction at a given Allergen Challenge visit, the patient's time will be censored at 24 hours. Kaplan-Meier estimates and curves will be produced for each visit.

The presence or absence of any asthma exacerbation (EAR or LAR) in the REGN1908-1909 treatment group as compared to placebo will be tested using a Fisher's Exact Test.

Individual spaghetti plots and mean plots of the percent change in FEV1 over time will also be examined. LOCF will be used in the calculation for any graphical displays of the mean change in FEV1 over the Cat Allergen Challenge.

The peak TNSS and TOSS and change from pre-challenge baseline to peak TNSS and TOSS across EEU challenge visits may also be examined using MMRM models.

The change and percent change from the Baseline Cat Allergen Challenge in the Fractional exhaled Nitric Oxide (FeNO) (adjusted for the pre-challenge baseline) will be explored using an MMRM model, with the treatment, visit, and treatment by visit interaction, and use of steroid rescue medications within 24 hours of the EEU challenge as factors. The time in EEU will be included as a covariate in the model.

The skin prick test with serial allergen titration with cat allergen will also be compared between treatment groups using an MMRM model, with the treatment, visit and treatment by visit interaction as factors.

5.6.4. Adjustment for Multiple Comparison

There is no adjustment for multiplicity for the primary or secondary efficacy variables.

5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.3.

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

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

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

5.7.1. Adverse Events

The verbatim text, the PT, and the primary SOC will be listed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

AEs will also be summarized by relationship to EEU procedure. Also, asthma related AEs, specifically, reported throughout the study will be presented for each treatment group and will be summarized by relationship to EEU procedure. Medications used to treat any asthma related AEs will also be listed and summarized by treatment group.

Period of observation: The observation period will be divided into two segments: pre-treatment and treatment periods. The pre-treatment period is defined as the time between when the subjects

give informed consent to before the single dose of study drug. The on-treatment period is defined as the time after the single dose of study drug until the end of study (week 16).

Day 1 is the first day of investigational product, Day –1 is the day before, and there is no Day 0.

Pre-treatment AEs are defined as AEs that developed or worsened during the pre-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the treatment period.

The focus of adverse event reporting in the clinical study report will be on TEAEs.

For details on handling missing data and partial dates, see Section 6.

Summaries of all TEAEs in each treatment group will include:

- All TEAEs by system organ class
- Possibly related TEAEs by system organ class
- Possibly related TEAEs by intensity and SOC (recommended)
- Time to first occurrence of any (or selected) TEAE (optional)
- Alert terms: all and possibly related TEAEs (optional)
- Serious adverse events: All and possibly related TEAEs by seriousness criterion
- Serious adverse events: All and possibly related TEAEs by SOC
- Death: All and possibly related TEAEs by SOC
- Other significant adverse events: All and possibly related TEAEs by "other significant" adverse event criterion
- Discontinuation: All and possibly related TEAEs by system organ class
- Non-serious possibly related TEAEs by SOC (mandatory if study includes a German center)

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the safety population in each treatment group.

Primary SOCs will be sorted according to the order described in the Guideline on summary of product characteristics (December 1999, European commission), with the total overall classes coming first and labeled "Any class". Within each primary SOC, PTs will be sorted by decreasing frequency of investigational product.

A second type of table with counts of each primary SOC in decreasing order of frequency will be provided. A third type of table with counts of each PT in decreasing order of frequency will also be provided.

Common TEAEs (preferred terms ≥1% in any treatment group) and very common TEAEs (preferred terms ≥5% in any treatment group) will be summarized in the report.

The description of very common TEAEs will also be performed for demographic factors including: gender, age (<65, >=65), and race.

5.7.2. Clinical Laboratory Measurements

A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but clinically significantly abnormal after treatment with investigational product, or a laboratory value that was abnormal at Baseline and exacerbates after treatment with investigational product. "Exacerbations" will be identified by the Medical Monitor using clinical judgment.

Baseline clinical laboratory analytes and change from Baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum. The graphs of mean (or median) value of some lab parameter vs. visit will also be plotted.

5.7.3. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate, and oximetry) will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

A summary of PCSVs will be constructed. Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory test of interest.

5.7.4. Analysis of 12-Lead ECG

ECG parameters (P-R interval ,QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be summarized at Baseline by treatment group.

5.7.5. Physical Exams

The number (n) and percentage (%) of subjects with abnormal, clinically significant physical exams will be summarized at each scheduled assessment time by treatment. Listings of physical examinations will be provided, including comments if examination was not performed. Listings of clinically significant abnormal physical examinations for each patient will be provided, along with comments from the investigator describing these abnormalities. These abnormalities will be organized into physical system classifications.

5.8. Analysis of Pharmacokinetic Data

Descriptive statistics of total REGN1908, total REGN1909 and total antibody (REGN1908+REGN1909) at each sampling time will be provided. Plots of mean concentrations versus time will be presented.

5.9. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Analysis described in this section will be performed separately for ADA against REGN1908 and ADA against REGN1909 in all treatment groups unless otherwise specified.

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

ADA response categories:

- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as a positive response in the ADA assay post dose when baseline results are negative or missing.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent, and treatment-boosted ADA response.

5.9.1. Association of Immunogenicity with Exposure, Safety and Efficacy

Immunogenicity and Exposure

Potential association between ADA variables and systemic exposure to REGN1908 or REGN1909 will be explored separately by treatment groups. Plots of drug concentration may be provided for analyzing the potential impact of ADA response status and titer on PK.

Immunogenicity and Safety and Efficacy

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

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

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

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

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.

Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive patients:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

5.10. Analysis of Biomarker Data

All biomarker analyses will be performed on the FAS using all observed data. Descriptive statistics for the observed values and change and percent change from baseline in detectable IgE (or percent of detectable IgE compared to baseline) by treatment and visit will be provided for the biomarker variables.

The percent of detectable IgE at each visit compared to baseline, and the ratio of Fel d 1 IgE to Cat Dander IgE at baseline will also be correlated to the primary and secondary clinical efficacy endpoints using Spearman's rho test. Both the Spearman correlation coefficients and p-values will be reported.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

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

If the scheduled Baseline Day 1 measurements are not available, screening assessments may be used.

6.2. Data Handling Convention for Efficacy Variables

Algorithm for Calculation of Area Under the Curve (AUC)

The AUC for the FEV1, TNSS, and TOSS for each Cat Allergen Challenge will be calculated using the trapezoidal rule. For each patient at each EEU visit, the AUC will be calculated over the time period of 0 to 2 hours. For example, the AUC will be calculated using the formula:

$$AUC_{[0-2\ hr]} = \left[\sum_{i=1}^{12}(t_i - t_{i-1}) * (D_i + D_{i-1})/2\right]/(t_{12} - t_0)$$

Where

- D_i is the FEV1, TNSS or TOSS value obtained at time t_i
- t_i is the time (in hours) for which D_i is measured, such as $t_0 = 0$, $t_1 = 1/6$ hour, $t_2 = 2/6$ hour, $t_3 = 3/6$ hour, $t_4 = 4/6$ hour, …, $t_{12} = 2$ hours.

If the patient remains in the EEU for less than 2 hours, LOCF will be used to impute values out to 2 hours. In the case of missing FEV1 measurements at one or more time points at a visit while the patient is in the EEU, linear interpolation will be used to impute missing values.

Additional analyses will be performed where the LOCF will be used to impute values out to 4 hours, where i ranges from 0 to 24. Also, the AUC will be calculated over the time while the patient is in the EEU, where the maximum value of i corresponds to the timepoint of the last spirometry effort performed in the EEU to provide the average FEV1 value during EEU exposure.

6.3. Data Handling Convention for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.5.1 and Section 4.5.2.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

To determine whether a medication is prior or concomitant, the missing medication start date is estimated as early as possible up to randomization date, and the missing medication end date is

estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

If a baseline value is missing for an efficacy endpoint, the patient will be excluded from analyses involving a change or percent change from baseline.

Adverse event

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

6.4. Data Handling Conventions for Biomarker Data

The following analysis conventions will be used in the statistical analysis:

a) The baseline measurement will be the last measurement prior to dosing. If patients are missing baseline data, the values obtained at screening will be used.
b) For data points above ULQ (e.g. for results reported as >XX), the ULQ plus one significant digit will be used.
c) For data points below LLQ (e.g. for results reported as <XX), 0.5X the LLQ will be used.

6.5. Visit Windows

Data analyzed by visit (including efficacy, laboratory data, vital signs, and ECG) will be summarized by the study scheduled visits described in the study protocol and SAP, "Schedule of Events". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination (ET) visit and end of treatment (EOT)/end of study (EOS) have the potential to be summarized.

6.6. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

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

7. INTERIM ANALYSIS

No formal interim analysis is planned.

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.

8. SOFTWARE

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

9. REFERENCES

1. Corren J, Patel D, Zhu J, Yegin A, Dhillon G, Fish JE. Effects of Omalizumab on Changes in Pulmonary Function Induced by Controlled Cat Room Challenge. J Allergy Clin Immunol 2011;127 (2) 398-405.
2. Gherasim A. Clinical Validation of Environmental Exposure Chamber in Strasbourg (Alyatec) in Asthmatic Patients Allergic to Cat Allerens. EAACI 2018 Poster Abstract 0994.
3. ICH. (1996, July 30). Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
5. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
6. Kleine-Tebbe J, Kleine-Tebbe A, Jeep S, Schou C, Lowenstein H, Kunkel G. Role of the major allergen (Fel d 1) in patients sensitized to cat allergens. Int Arch Allergy Immunol 1993;100 (3):256-62.
7. LaVange, L. M., & Koch, G. G. (2006). Rank score tests. Circulation, 114(23), 2528-2533.
8. Pfaar O, Calderon MA, Andrews CP, Angieli E, Bergmann KC, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future- an EAACI position paper. Allergy 2017; Jul; 72(7): 1035-1042.
9. van Ree R, van Leeuwen WA, Bulder I, Bond JF, Aalberse RC. Purified natural and recombinant Fel d 1 and cat albumin in in vitro diagnostics for cat allergy. J Allergy Clin Immunol 1999;104(6):1223-30.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Time to EAR	*FAS, PPS*	*Time to EAR (a 20 % drop in FEV1 or when the subject exits the EEU on day 8 due to clinically significant symptoms), censored at 4 hours if the patient does not experience an EAR*	*Cox proportional hazards model*	*Yes Kaplan Meier estimates and plots*	*No*	*Sensitivity Analysis: Fisher's exact test comparing the proportion of subjects with EAR*
Secondary Endpoints						
Time to EAR	*FAS, PPS*	*Time to EAR (a 20 % drop in FEV1 or when the subject exits the EEU on days 29, 57, and 85 due to clinically significant symptoms), censored at 4 hours if the patient does not experience an EAR*	*Cox proportional hazards model*	*Yes Kaplan Meier estimates and plots*	*No*	*Sensitivity Analysis: Fisher's exact test comparing the proportion of subjects with EAR*
AUC of FEV1	*FAS*	*Percent change in the AUC of FEV1 from baseline to days 8, 29, 57, and 85*	*MMRM*	*No*	*No*	*No*
AUC of TNSS	*FAS*	*Change in the AUC of TNSS from baseline to days 8, 29, 57, and 85*	*MMRM*	*No*	*Yes*	*No*

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
AUC of TOSS	*FAS*	*Change in the AUC of TOSS from baseline to days 8, 29, 57, and 85*	*MMRM*	*No*	*Yes*	*No*
Cat allergen quantity	*FAS*	*Change and percent change in cat allergen quantity as experienced by patients from baseline to days 8, 29, 57 and 85*	*MMRM*	*No*	*No*	*No*

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	*FAS*	*Percent of patients by system organ class*	*Descriptive Statistics*	*No*	*No*	*No*

10.2. Schedule of Time and Events

Table 1: Schedule of Time and Events

Study Procedure	**Screening[1]**				**Randomization and Treatment Period**									**End of Study/Early Termination Visit**	**Unscheduled Visit[24]**
Visit	**V1[25]**	**Placebo EEU V2[25]**	**Cat EEU[3,22] V3**	**V4**	**R[2] V5**	**Cat EEU[22,23] V6**	**Tel.**	**Cat EEU[22] V7**	**V8**	**Cat EEU[22] V9**	**Tel.**	**Cat EEU[22] 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**	
Screening/Baseline															
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 allergen [4]	X														
Skin prick test for other common allergens[4]	X														
Placebo challenge		X													

Study Procedure	**Screening[1]**				**Randomization and Treatment Period**									**End of Study/Early Termination Visit**	**Unscheduled Visit[24]**
Visit	**V1[25]**	**Placebo EEU V2[25]**	**Cat EEU[3,22] V3**	**V4**	**R[2] V5**	**Cat EEU[22,23] V6**	**Tel.**	**Cat EEU[22] V7**	**V8**	**Cat EEU[22] V9**	**Tel.**	**Cat EEU[22] 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**	
Screening Cat Allergen Challenge[3]			X												
Spirometry[5] (includes FEV1)	X	X	X	X	X										
Minute ventilation	X														
Treatment															
Randomization[2]					X										
Administer Study Drug[2]					X										
Cat Allergen Challenge [3]						X		X		X		X			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy															
TNSS nasal symptoms score[6]			X	X		X		X	X	X		X	X	X	
TOSS ocular symptoms score[6]			X	X		X		X	X	X		X	X	X	
Chest symptoms questions[6]			X	X		X		X	X	X		X	X	X	
Spirometry (includes FEV1)[5]						X		X	X	X		X	X	X	
PNIF[7]			X			X		X		X		X			

Study Procedure	**Screening[1]**				**Randomization and Treatment Period**									**End of Study/Early Termination Visit**	**Unscheduled Visit[24]**
Visit	**V1[25]**	**Placebo EEU V2[25]**	**Cat EEU[3,22] V3**	**V4**	**R[2] V5**	**Cat EEU[22,23] V6**	**Tel.**	**Cat EEU[22] V7**	**V8**	**Cat EEU[22] V9**	**Tel.**	**Cat EEU[22] 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**	
Skin Prick Test with Serial Allergen Titration (Cat-SPT)[8]			X					X				X		X	X
FeNO[9]		X		X					X				X		
Safety[10]															
Vital Signs	X	X[12]	X[12]	X	X[11]	X[12]		X[12]	X	X[12]		X	X	X	X
Physical Examination	X		X[27]		X	X[27]		X[27]		X[27]		X[27]		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[20]		X[21]	X[20]		X[20]		X[20]		X[20]			
Distribution of rescue treatment kit			X			X		X		X		X			
Telephone Call[13]							X				X				
Laboratory Testing[14]															
Hematology	X				X[15]			X		X		X		X	X
Blood Chemistry	X				X[15]			X		X		X		X	X
Urinalysis	X				X			X		X		X		X	X
βHCG serum pregnancy test	X														X

Study Procedure	**Screening[1]**				**Randomization and Treatment Period**									**End of Study/Early Termination Visit**	**Unscheduled Visit[24]**
Visit	**V1[25]**	**Placebo EEU V2[25]**	**Cat EEU[3,22] V3**	**V4**	**R[2] V5**	**Cat EEU[22,23] V6**	**Tel.**	**Cat EEU[22] V7**	**V8**	**Cat EEU[22] V9**	**Tel.**	**Cat EEU[22] 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**	
Urine pregnancy test (for female patients only)[16]		X	X		X[16]	X		X		X		X		X	X
FSH test (in postmenopausal women only)[28]	X														
Serum for specific IgE for Fel d 1 and cat allergen	X		X		X	X		X		X		X			
Serum for sIgE (Fel-D 2, 4, 7) tests[17]			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[26]			X					X							
Genomic DNA sample[18]					X										
PK[19] and ADA															

Study Procedure	Screening[1]				Randomization and Treatment Period									End of Study/Early Termination Visit	Unscheduled Visit[24]
Visit	V1[25]	Placebo EEU V2[25]	Cat EEU[3,22] V3	V4	R[2] V5	Cat EEU[22,23] V6	Tel.	Cat EEU[22] V7	V8	Cat EEU[22] V9	Tel.	Cat EEU[22] 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	
Drug conc. sample					X[15]	X[19]		X		X		X		X	X
ADA sample					X[15]							X		X	X

10.2.1. 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 allergen and skin prick testing for other common allergens is performed as described in the study manual. If screening skin prick test for cat allergen 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 allergen 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 (±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

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

Parameter	PCSV For Studies in healthy subjects only	Comments
AST	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	> 1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008
Total Bilirubin	> 1.5 ULN > 2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Concept paper on DILI – FDA draft Guidance Oct 2008 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 To be counted within the same treatment phase, whatever the interval between measurement
CPK	> 3 ULN >10 ULN	FDA Feb 2005 Am J Cardiol April 2006 Categories are cumulative First row is mandatory. Rows following one mentioning zero can be deleted.
Creatinine	≥ 150 µmol/L (adults) ≥ 90 µmol/L (6-12 year-old) ≥ 30% from baseline ≥ 100% from baseline	Benichou C., 1994

Parameter	PCSV For Studies in healthy subjects only	Comments
Creatinine Clearance (Cockcroft's formula)	< 30 ml/min (severe renal impairment) ≥30 - < 50 ml/min (moderate renal impairment) ≥50 - ≤ 80 ml/min (mild renal impairment)	Use is optional. FDA criteria May 1998
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed. 2008
Sodium	≤129 mmol/L ≥ 160 mmol/L	
Potassium	< 3 mmol/L ≥ 5.5 mmol/L	FDA Feb 2005
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)	Threshold for therapeutic intervention
Triglycerides	≥ 4.6 mmol/L (4 g/L)	Threshold for therapeutic intervention
Glucose Hypoglycaemia Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 7 mmol/L (fasted); ≥ 11.1 mmol/L (unfasted)	 ADA May 2005 ADA Jan 2008
CRP	> 2 ULN or >10 mg/L, if ULN not provided	FDA Sept 2005
Hematology		
WBC	< 3.0 Giga/L (3000/mm3) < 2.0 Giga/L (2000/mm3) (Black)	Increase-in WBC: not relevant To be interpreted only if no differential count available.
Neutrophils	< 1.5 Giga/L (1500/mm3) < 1.0 Giga/L (1000/mm3) Black	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Eosinophils	> 0.5 Giga/L (500/mm^3) or > ULN if ULN ≥ 0.5 Giga/L	Gallin 1989, Harrisson 13th Ed, 1994.
Hemoglobin	At least 20 g/L (1.24 mmol/L) decrease versus baseline	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥ 30 g/L, ≥ 40 g/L, ≥ 50 g/L)
Platelets	< 100 Giga/L (100 000/mm^3)	International Consensus meeting on drug-induced blood cytopenias, 1991.
Vital signs		
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	Proposed change: To be are applied for all position (including missing) except STANDING
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 140 mmHg and increase from baseline ≥ 20 mmHg	Proposed change: To be are applied for all position (including missing) except STANDING
DBP	Young and elderly subjects ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 90 mmHg and increase from baseline ≥ 10 mmHg	Proposed change: To be are applied for all position (including missing) except STANDING
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg	
Weight	≥ 5 % increase versus baseline ≥5% decrease versus baseline	FDA Feb 2007
ECG parameters		CPMP 1997 guideline

Parameter	PCSV For Studies in healthy subjects only	Comments
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	
PR	≥ 220 ms	
QRS	≥ 120 ms	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Males Females Borderline 431-450 ms 451-470 ms Prolonged* > 450 ms > 470 ms QTc ≥500 ms ≥ 500 ms <u>Increase versus baseline</u> (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms	To be applied to any kind of QT correction formula *QTc prolonged and ΔQTc > 60 ms are the PCSA to be identified in individual subjects/patients listings.