A Single Dose Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of REGN1908-1909 in Allergic Rhinitis Patients Challenged Intranasally with Allergen Extract

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Primary objective: to assess the inhibition of allergic responses of a single dose of subcutaneously (SC) administered REGN1908-1909 as measured by total nasal symptom score (TNSS), visual analog scale (VAS) nasal symptoms score, and peak nasal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON40738

Source
ToetsingOnline

Brief title
R1908-1909-ALG-1325, cat allergy study

Condition

- Allergic conditions
- Upper respiratory tract disorders (excl infections)

Synonym
allergic rhinitis, cat allergy

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: Allergic Rhinitis, Efficacy, Pharmacokinetics, REGN1908-1909, Safety, Tolerability

Outcome measures

Primary outcome

Change in TNSS AUC between day 8 and pretreatment NAC over the first hour of

the challenge (0 hour to hour 1).

Secondary outcome

- Change from pretreatment NAC to days 29, 57, and 85 in TNSS AUC over the

first hour of the initial challenge (0 hour to hour 1)

- Change from pretreatment NAC to days 8, 29, 57, and 85 in TNSS AUC during

hour 1 to hour 8 of the initial challenge

- Incidence rates of treatment-emergent adverse events (TEAEs) and serious

TEAEs through day 85 in subjects treated with a single 600 mg SC dose of

REGN1908-1909 or placebo

- Characterization of the key PK parameters of REGN1908 and REGN1909 following

SC coadministration at a 1:1 ratio.

Study description

Background summary

Cat allergy is a prominent cause of rhinoconjunctivitis and allergic asthma and is highly prevalent in westernized countries. Cat-allergic individuals experience symptoms such as sneezing, rhinorrhea, nasal itching, nasal

congestion, conjunctivitis and/or asthma when exposed to cats or cat dander. These symptoms are persistent in patients with continuous cat exposure, and can be severe even in patients with episodic exposures.
Felis silvestris catus (domestic cat) allergen 1 (Fel d 1) is the immunodominant cat allergen; it is inhaled due to its association with cat dander particles and it elicits immunoglobulin E (IgE) mediated allergic responses in 90% to 95% of patients with cat allergy. Fel d 1 accounts for 60% to 90% of the total allergenic activity in cat allergen extract. Most first-line allergy treatments target the symptoms of disease. Rhinoconjunctivitis
symptoms are treated with antihistamines and intranasal steroids, which are only moderately effective. Despite the widespread availability of allergy treatments, patient dissatisfaction with current allergy therapies results in an unmet need for novel therapies.

REGN1908 and REGN1909 are high-affinity monoclonal antibodies (mAbs) that bind distinct epitopes on Fel d 1 in a non-competitive manner. The 1:1 mixture of these two antibodies demonstrated an inhibitory effect on allergic response to Fel d 1 in a murine model of allergy, which was superior to the inhibitory effect of either antibody alone. Therefore, REGN1908 and REGN1909 will be clinically tested as a mixture (designated as REGN1908-1909). REGN1908-1909 may provide therapeutic benefit for patients with cat allergy whose symptoms are not managed effectively with current therapies.

Study objective

Primary objective: to assess the inhibition of allergic responses of a single dose of subcutaneously (SC) administered REGN1908-1909 as measured by total nasal symptom score (TNSS), visual analog scale (VAS) nasal symptoms score, and peak nasal inspiratory flow (PNIF) in cat-sensitized allergic rhinitis subjects challenged intranasally with cat hair extract (NAC).
Secondary objectives:
* To assess the safety and tolerability of a single dose of SC administered REGN1908-1909 in cat-sensitized allergic rhinitis subjects.
* To assess the pharmacokinetic (PK) profile of REGN1908-1909 following single-dose SC administration

Study design

This is a phase 1b, randomized, double-blind, placebo-controlled, single dose, proof-of-mechanism study to evaluate the efficacy of pretreatment with a single SC dose of REGN1908-1909 in the inhibition of allergic response to a NAC by passive immunization. Approximately 70 cat-sensitized subjects diagnosed with cat-induced allergic rhinitis will be enrolled, based on a positive response to NAC with cat hair extract, and randomized 1:1 on day 1 to receive 600 mg REGN1908-1909 or placebo administered SC. Subject randomization will be

stratified to 2 blocks: the London site (Quintiles Phase I Unit), and all other study sites combined.

Subjects will undergo screening at 2 visits: on day -28, and on day -14 (+/- 2 days).
At screening visit 1 (day -28), subjects will undergo the informed consent process, and a skin prick test with cat hair and other allergen extracts to confirm sensitization to respective allergens, allergen-specific IgE tests for a panel of allergens, and standard screening procedures will be performed.

Pretreatment/Screening NAC
At screening visit 2 (on day -14 [+/- 2 days]), a single NAC with cat hair extract will be performed. Total nasal symptom score (measured on a 0 to 12 scale) is based on assessment of 4 symptoms graded on a 0 (none) to 3 (severe) scale for congestion, itching, and rhinorrhea, and 0 (none) to 3 (5 or more sneezes) for sneezing, and will be used as a primary readout of the allergic response. In addition to TNSS, VAS nasal symptoms score (measured on a 0 [no symptoms] to 100 [maximum nasal symptoms] scale) and PNIF (measuring nasal patency [l/min]) will be used to assess allergic response to NAC at multiple timepoints, as described in the study manual.

Subjects must have TNSS *2 prior to NAC (at 0 hour) and peak TNSS *7 induced by NAC within the first hour (0 hour to hour 1) at the screening NAC, to be eligible for randomization on day 1.

The TNSS, VAS nasal symptoms score, and PNIF measurements obtained at the screening NAC visit will be considered a baseline response and used for efficacy assessments at the post REGN1908-1909 treatment time-points.

Day 1 Treatment
On day 1 (baseline), eligible subjects will be randomized to receive a single SC administration (as 3 injections) of blinded study drug (REGN1908-1909 mixture) at a total dose of 600 mg (300 mg of each mAb) or placebo.

Post REGN1908-1909 Treatment NACs (Days 8, 29, 57, and 85)
On days 8 (+/- 2 days), 29 (+/- 2 days), 57 (+/- 3 days), and 85 (+/- 3 days), following REGN1908-1909 treatment, an NAC with the same increasing doses of allergen as at the screening NAC visit (day -14 [+/- 2 days]) will be conducted regardless of the TNSS values recorded over the course of allergen titration. The allergen titration will proceed to the screening provocation dose (the allergen dose that was required to achieve
to achieve TNSS >7 at the screening visit).
A cat hair skin prick test will be repeated at the day 29 and day 85 visits.

In addition to TNSS, a VAS nasal symptoms score (measured on a 0 to 100 scale) and PNIF (l/min) will be used to assess response to NAC.
Visual analog scale nasal symptoms scores will be assessed on the day of the

screening NAC visit (day -14 [+/- 2 days]), and on days 8, 29, 57, and 85 at multiple timepoints during NAC visits, as described in the study manual.

Peak nasal inspiratory flow (l/min) will be measured by a nasal spirometer at the screening NAC visit (day -14 [+/- 2 days]), and on days 8, 29, 57, and 85 at multiple timepoints during NAC visits, as described in the study manual.

Subjects will complete the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) to assess the subjective impact of allergic symptoms on quality of life. Scores will be assessed at the screening visit (day -28) and on days 1, 8, and 85 (end of study) or at the time of early termination.

Nasal secretion samples will be collected at the screening NAC visit (day -14 [+/- 2 days]), and on days 8, 29, 57, and 85. Nasal secretions will be collected following nasal lavage but prior to the initial challenge (0 hour) and at 15, and 30 minutes, and 1, 2, 4, 6, and 8 hours postallergen challenge. The nasal secretion samples will be collected after the TNSS, PNIF and VAS nasal symptoms score assessments are completed.
Samples for safety laboratory analysis will be obtained at screening (day -28), on day 1 (prior to drug administration), and on days 29, 57, and 85 (end of study) or at the time of early termination.

Blood samples for the determination of total REGN1908 and REGN1909 in serum will be collected on day 1 (prior to drug administration), and on days 4, 8, 29, 57, and 85 (end of study) or at the time of early termination. Anti-drug (anti-REGN1908 and anti-REGN1909) antibody (ADA) samples (serum) will be collected on day 1 (prior to drug administration), and on days 29, 57, and 85 (end of study) or at the time of early termination.

Serum samples for measurement of total immunoglobulin E levels (IgE) and allergen-specific IgE levels (IgE specific for Fel d 1, Fel d 2, cat dander, galactose-1, 3-alpha-galactose and a panel of common regional allergens) and exploratory antibody measurements will be collected
during screening (on day -28), on day 1 (prior to drug administration), and on days 8, 29, 57, and 85 (end of study) or at the time of early termination.

Serum and plasma samples for exploratory research will be collected during screening (on day -14 [+/- 2 days], prior to the screening NAC), and on day 1 (prior to administration of study drug), day 8, 29, 57, and 85 (end of study) or at the time of early termination. Whole blood samples for exploratory RNA analysis will be collected on day 1 (prior to administration of study drug) and day 8. Whole blood samples for exploratory immunomonitoring assays, including basophil histamine release (BHR) and basophil activation test (BAT) will be collected on the screening NAC day (day -14 [+/- 2 days]), on day 1 (prior to study drug administration), and on days 8, 29, and 85 (end of study) or at the time of early termination. Samples will be collected prior to NAC or study drug administration. This analysis will be restricted to subjects enrolled at the

study site in
London (Quintiles Phase I Unit). A genomic DNA sample will be collected at the day 1 visit (or at any other study visit) from subjects who have consented to the optional pharmacogenomics substudy. Information on adverse events (AEs) and concomitant medications will be collected from the time of informed consent through day 85 (end of study), or until the time of early termination.

Intervention

Subcutanous injection with IP, intranasal challenge to Allergic Rhinitis with Allergen Extract, Skin Prick Test, venapunction, questionaires.

Study burden and risks

Allergic reaction (could be severe).
Formation of antibodies towards study drug.
Discomfort from the skin prick procedure; local reaction at site, symptoms such as itching all over the body, sneezing, and eyelid swelling (1 per 10,000 people) or anaphylactic shock that can be fatal (very rare).
Blood draws; discomfort from needle stick (frequently), bruising at site of needle stick (infrequent), infection at needle stick site (rare) or fainting or dizziness (infrequent).
Unforeseeable or unknown risks: e.g. to the unborn child or cancer.

Contacts

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Scientific
Regeneron Pharmaceuticals, Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Generally healthy men and women between the ages of 18 and 55, inclusive;
2. Body mass index (BMI) between 18.0 kg/m2 and 32.0 kg/m2, inclusive;
3. History of allergic rhinitis which is exacerbated by exposure to cats;
4. Cat sensitization confirmed at screening by both: i) positive skin prick test with cat hair extract (mean wheal diameter at least 3mm greater than negative control) ii) positive allergen-specific IgE tests for cat dander and Fel d 1 *0.35 kAU/l for both allergens);
5. Positive NAC (which is defined as a peak TNSS score >7 [on a 12-point scale], and with a prechallenge TNSS *2) upon nasal allergen challenge with cat hair extract at screening
6. Normal lung function as judged by the investigator. Asthma subjects must have forced expiratory volume in 1 second (FEV1) * 80% of expected value at screening.
7. Willing and able to comply with clinic visits and study-related procedures
8. Provide signed informed consent
9. Able to understand and complete study-related questionnaires

Exclusion criteria

1. Persistent chronic or active recurring infection requiring treatment with antibiotics, antivirals, or antifungals or untreated respiratory infections within 4 weeks prior to the screening visit.
2. Serum creatinine, 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
3. Any clinically significant physical exam abnormalities observed during the screening visit
4. Any gross mechanical nasal obstruction, or history of nasal or sinus surgery that may interfere with the conduct of the NAC as per judgment of the Investigator.
5. Use of any concomitant medications within 3 weeks of the screening visit including antihistamines, leukotriene inhibitors, mast cell inhibitors, topical corticosteroids

including intranasal corticosteroids, oral or topical decongestants, topical calcineurin inhibitors, beta blockers, nutritional supplements, over-the-counter medications, and use of systemic corticosteroids within 12 weeks.
6. Use of anti-IgE therapy within 6 months prior to screening.
7. History of SIT with cat allergen and vaccines against cat allergy
8. SIT with any allergen within 3 months prior to screening
9. Habitation in a household with 1 or more cats or chronic exposure to cats within 3 months prior to the screening visit and during the duration of the study
10. Subjects with grass, tree, or Artemesia sensitization (confirmed at screening by both a positive skin prick test and a positive allergen-specific IgE test [> 0.35 kAU/l] for respective allergens) may only be enrolled at the end of regional pollen season and at the discretion of the investigator. Note: In view of regional variations on allergen exposure, the appropriate seasonal allergen will be tested.
11. Subjects who anticipate major changes in allergen exposure in their home or work environments during the course of the study as assessed by the Investigator.
12. Subjects receiving therapy with any agents known or likely to interact with adrenaline (eg, beta blockers, ACE-inhibitors, tri-cyclic antidepressants, or other drugs), within 3 weeks prior to screening
13. Hospitalization for any reason within 30 days of the screening visit
14. Asthma requiring chronic treatment (except asthma subjects treated with intermittent salbutamol) or atopic dermatitis requiring treatment with topical or systemic corticosteroids and/or calcineurin inhibitors within 6 months prior to screening
15. Human immunodefieciency virus (HIV) infection or HIV seropositivity at the screening visit
16. Positive hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit
17. Known sensitivity to doxycycline or to any of the components of the Investigational Product formulation
18. History of severe asthmatic reaction or anaphylaxis after exposure to cats
19. Participation in any clinical research study evaluating another investigational drug or therapy within 90 days or at least 5 half-lives (whichever is longer) of the investigational drug prior to the screening visit
20. Positive serum hCG pregnancy test at the screening visit
21. Pregnant or breastfeeding women
22. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly)
*Contraception is not required for men with documented vasectomy.
**Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n/a
Generic name:	REGN1908-1909

Ethics review

Approved WMO Date:	20-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-09-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004950-68-NL
CCMO	NL49085.056.14
Other	U1111-1155-2258