ANG22-01H STUDY

An open label, safety and allergenicity Phase 0 study of a new hypoallergenic plant-derived cat dander biologic in adult cat allergic subjects

CLINICAL SUMMARY REPORT

Non-ICH Format

Version 3.0 (April 28, 2024)

- **Official study start date:** Sept 19, 2023 (FPFV)
- **Official study end date:** Dec 11, 2023 (LPLV)
- **Clinical site:** Royal Brompton Hospital (RBH), London, UK
- **Chief Clinical Investigator:** Guy Scadding, MD, PhD (RBH)
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1.0 Introduction

Allergy to cats ranks second place amongst allergies to indoor allergens, after house dust mites. If outdoor allergens are taken into account, only pollens rank above cats. Sensitization to cat allergens is very common, ranging from 10-15%. Among patients with respiratory allergies, up to around one-third are sensitized to cats. By far, the most important allergen for cat allergy is Fel d 1, with up to> 90% of patients being sensitized to it. Moreover, of the total IgE response to cats, between 60% and 90% is directed to Fel d 1. Hence, allergen-specific treatment for cat allergy with Fel d 1 as the sole active ingredient is expected to be sufficient for most cat-allergic individuals.

In houses with cats, environmental Fel d 1 levels can be very high, and removal of the animals may effectively reduce the level of exposure by up to around 100-fold, but many cat owners are reluctant to do so. Moreover, Fel d 1-carrying particles in house dust prove to be quite sticky and travel on clothes to public places devoid of cats, such as schools and workplaces, resulting in often immunologically relevant environmental exposure. Since around 25% of Fel d 1 is found on particles of <5 µm, the allergen does not only reach the upper airways, but also easily reaches the lower airways. Together, these properties make cat, in particular Fel d 1 sensitization a major risk factor for respiratory allergic diseases, including severe, potentially life-threatening allergic asthma.

Pharmacological treatment options have mostly centered on the use of symptoms alleviating medications (antihistamines, topical nasal steroids and/or inhalers) which do not affect the progression of the disease. Desensitization can help a significant number of cat-allergic individuals, yet the associated risks and difficult logistics make it so that only a very small percentage (probably less than 2%) of people allergic to cats truly benefit from it.

Type I allergic diseases such as allergic rhinoconjunctivitis (ARC), asthma, and food allergy are IgE-mediated chronic inflammatory diseases. Respiratory allergies can either be seasonal (e.g., pollen hay fever) or perennial (e.g., asthma caused by house dust mites or pets). Treatment of ARC and allergic asthma is heavily dominated by symptomatic medication such as antihistamines and local or systemic corticosteroids. For ARC and to a lesser extent for allergic asthma, allergen immunotherapy (AIT) aka as desensitization, is an established alternative treatment. It has already been in use for over a hundred years, first only in the form of subcutaneous injections (SCIT), more recently also as sublingual drops or tablets (SLIT).

The active ingredients used for desensitization are almost always crude extracts of the allergen sources; in case of SCIT often in combination with an adjuvant (e.g., aluminum hydroxide). Although it is the only disease-modifying treatment that offers the possibility of sustained efficacy, even after discontinuation, AIT only has a niche position with <10% of the treatment market.Two major reasons can account for this: 1) the treatment is long and intensive, with either monthly injections (SCIT) or daily drops/tablets (SLIT) for 3–5 years, and 2) allergic side-effects are common, and occasionally severe. Over the last decades, many attempts have been made to improve the performance of AIT, both with respect to efficacy and safety. Most attention was given to replacing allergen extracts by recombinant versions of their major allergens, either as wild-type molecules or as hypoallergenic derivatives such as full-length mutants, as peptides representing T- and/or B-cell epitopes or as chemically modified versions. Although several of these approaches have been successful to varying degrees up to Phase 2 clinical trials, none has achieved market authorization, either because Phase 3 studies failed or because they offered no significant improvement over classical extract-based products.The scientific evidence supporting the efficacy of extract-based cat allergy immunotherapy is for the most part relatively dated.

Individuals who are allergic have an inappropriate Th2 response to harmless environmental substances resulting in the production of IgE antibodies to these allergens with the ensuing inflammatory response upon re-exposure to the allergen. The objective of immunotherapy is to direct the immune response away from a Th2-driven IgE-dominated humoral immune response towards a protective anti-inflammatory Th1/Treg-driven IgG1/IgG4-dominated one thereby encouraging the body to produce fewer IgE antibodies and more Th1 and T regulatory cells that secrete Il-10 and TGF which skews the response away from IgE production and induces production of allergen-specific IgGs which is essential for the neutralization of allergens brought by subsequent exposures. Allergen-specific IgG antibodies also block various IgE-mediated processes and interfere with IgE-mediated basophil degranulation.

While allergens used in AIT and SLIT methods are capable of inducing an effective and strong Treg/Th1-driven protective blocking IgG response, a greater efficacy and safety, shorter onset of action and longer disease remission are still required in cat allergy immunotherapy. A promising new strategy is to present major allergens in the context of nanoparticles such as liposomes or virus-like particles. Presentation of major allergens on nanoparticles is expected to increase their immunogenicity, a prerequisite to increase efficacy and anticipated to reduce treatment duration and/or frequency. Furthermore, *in vitro* experiments with virus-like particles surface-expressing allergens have demonstrated that they behave like hypoallergenic structures. The interpretation is that high-density presentation does not favor cross-linking of IgE on mast cells and basophils, the effector cells of the allergic response.

Angany has developed a unique plant-based manufacturing process to produce biosynthetic nano-particles displaying thousands of copies of a specific allergen on their surface (eBioparticles™). These eBioparticles demonstrate the potential to trigger a strong Th1/Treg-driven blocking IgG-immune response. These eBioparticles, including Fel d 1-eBPs, are both hypoallergenic and hyperimmunogenic and as such, a Fel d 1-eBP biologic is a potentially safe and effective approach for immunotherapy for cat allergy.

The active ingredient of the Fel d 1-eBP biologic candidate is an *in vivo* synthesized enveloped bioparticle that presents multiple copies of Fel d 1 on its surface. Like other enveloped viruses or virus-like particles (such as influenza or coronavirus virus-like particles (VLPs), Fel d 1-eBPs are synthesized by the assembly and budding of transmembrane protein ultrastructures at the surface of recombinant host cells. In the case of Angany's Fel d 1-eBPs, the host cell system of choice is *Nicotiana benthamiana*.

2.0 ANG22-01H study synopsis

Name of Sponsor/Company: Angany Inc.
Name of Investigational Product: ANG101
Nature of Product: Fel d 1-eBP biologic
Active Ingredient: Fel-d-1 bioparticles colloidal solution which contains 33 ug/mL of a recombinant version of the major allergen of cat allergy Fel d 1 produced in the *Nicotiana benthamiana* plant system.
Title of Study: An open label, safety and allergenicity Phase 0 study of a new hypoallergenic plant-derived cat dander vaccine in adult cat allergic subjects

Study centre: Allergy and Clinical Immunology, Royal Brompton Hospital, London, UK

Overall study period (months): 3	**Phase of development:**
Date first patient first visit: September 19, 2023 Date last patient completed: Dec 11, 2023	Exploratory—Phase 0

Overall study objectives:

The overall aim of this Phase 0 study is to determine the preliminary safety and allergenicity of ANG101 in adult subjects with cat allergic rhinitis/rhinoconjunctivitis with or without mild to moderate (controlled) asthma. Study objectives will be met through the use of a standard diagnostic Skin Prick Test (SPT) as well as the Intradermal Skin Test (IDT).

Study objectives:

1. To assess the preliminary safety of ANG101 on skin prick and intradermal testing
2. To measure the degree of allergenicity of ANG101, in comparison to a Fel d 1—containing commercial cat dander extract diagnostic challenge test in a titrated SPT in adult cat allergic subjects
3. To evaluate the late phase immunological response at 6.5 hrs to intradermal injection of ANG101 (IDT)

Primary study endpoint:

Safety: general safety of the new vaccine in skin testing will be assessed by evaluating adverse events (AEs), vital signs (body oral temperature, respiratory rate, heart rate, and blood pressure) and if needed, physical examination.

Secondary endpoints:

Skin reactivity/allergenicity: The early phase skin response (wheal diameter) to ANG101 in a titrated SPT compared to a commercial cat dander allergen extract, will be evaluated. The primary outcome will be the provocation concentration of allergen that causes a ≥ 5 mm skin wheal. In addition to the early phase response, the late phase skin response following intradermal administration of Fel d 1-eBP will also be compared to the commercial extract at 6.5 hours post-injection.

The provocation concentration of allergen that causes a ≥ 3 mm skin wheal will also be determined, as a secondary endpoint.

***Ex vivo* allergenicity assessments on blood samples:**

- Basophil Activation Test (BAT)— to determine the percentage of basophils activated in response to ANG101 compared to a commercial cat dander extract.
- Diamine Oxidase (DAO) Test—to determine the potency of ANG101 to induce basophil histamine release compared to a commercial cat dander extract.

Study Design and Procedures:

This Phase 0 study is an exploratory, open label, non-randomised SPT/IDT evaluation involving subjects with a history of a minimum of two years cat-induced allergic rhinitis/rhinoconjunctivitis

with or without mild to moderate (controlled) allergic asthma.

At the screening visit (V0), all participants will have a medical history taken and a directed physical examination. FEV-1 will be measured first using appropriate spirometric equipment. Vital signs will be measured. SPTs (Soluprick HQ10, ALK Denmark) will be performed on the flexor aspect of one forearm with a panel of inhaled allergens including cat dander (in duplicate for eligibility assessment). Blood will be withdrawn for hematology, biochemistry, total IgE and allergen specific IgE (*ImmunoCAP* test) to whole cat allergen and major cat allergen Fel d 1. Blood samples will be obtained before SPTs are performed. Briefly, the following study procedures will be done in all subjects, as follows:

After an interval of a minimum of 7 days post screening (maximum 28 days), participants will return to the clinic in the morning (V1 visit). Use of prohibited meds will be verified. Vital signs will be measured. Extinction dilution SPTs will be performed in duplicate on the flexor aspect of both forearms (one arm for each product). Both the new experimental vaccine and commercial cat dander extract will be administered as successive dilutions of both products, ensuring equivalent concentrations of Fel d 1 allergen between the two products at each concentration. The respective Fel d 1 concentrations of the commercial extract (ALK Soluprick) and ANG101 are 41 and 33 µg/ml, respectively. Therefore, the following 6 dilutions of each product will be administered, in duplicate, ALK Soluprick: 1/1.2, 1/6, 1/60, 1/600, 1/6,000, 1/60,000; ANG101: undiluted, 1/5, 1/50, 1/500, 1/5,000, 1/50,000. Two additional SPTs will be performed as well: 1 for the inert negative control, and 1 for a histamine positive control. This gives a total of 14 tests on each forearm, one used for for ALK Soluprick and controls, and the other one for Fel d 1-BP and controls.

Individual wheal sizes will be recorded and the mean of 2 measurements will be used. SPTs will be performed without any lag time in each participant.

Early and late-phase (T cell dependent) response will also be tested following intradermal tests (IDT). After recording the extinction dilution SPT results, IDTs will be performed on the extensor surface of each forearm. 1/1000 and 1/100 dilutions of the provocation concentration of Fel d 1 allergen that caused a 3 mm skin wheal as judged by the previous same-day extinction dilution skin prick testing will be used for both Fel d1 eBP vaccine and commercial cat dander extract (on different arms).

If found to be sufficient and safe, then these same 2 doses will be given to the remaining participants.

The immediate test wheal size will be recorded at 15 minutes. Participants will remain in the allergy clinic, under clinical observation during 6.5 +/- 0.5 hours after the first IDT is performed, and will then undergo a late phase skin reaction evaluation, using a standard method. Patients will only be discharged after completion of all the safety assessments and if considered fit to leave the hospital.

A sentinel dosing strategy will be employed. A first group of three (3) subjects will complete all skin test procedures (SPTs and IDTs) as well as a 24-hour post-skin test safety follow-up. A minimum of 7 days will occur before initiating the skin tests in all remaining subjects. If the post IDT-skin reaction is not significant enough using the 1/1000 and 1/100 dilutions, then 1/100 an 1/30 dilutions will be used in 3 additional sentinel subjects, as well as in all remaining subjects.

In order to properly assess potential immediate and short-term adverse events, all patients will be closely monitored during 1 hour following all skin tests. Heart rate, blood pressure, body temperature, O_2 saturation and respiratory rate will be measured prior to SPT (at arrival) and 60 minutes after. Adverse events, if any, will be reported.

The Investigator will contact all subjects by phone approximately 24 hours following the end of the SPT/IDT session and again 7 days later to monitor for any adverse events and any changes in

concomitant medications. Study participants will also be able to contact the study site any time after discharge, to report any safety question or issue.

Patient Population

Adults with a history of a minimum of two years of cat induced allergic rhinitis/rhinoconjunctivitis with or without mild to moderate asthma.

Sample size:

Twenty (20) evaluable cat allergic subjects (including the 3 sentinel subjects)

Diagnosis and main criteria for inclusion and exclusion (abbreviated list):

Inclusion criteria

Subjects must meet the following criteria to be entered into the study:

1. Adults (male or female) aged 18–60 years.
2. Documented recent (2 years) history of cat-induced:
    a. Moderate to severe persistent allergic rhinitis or rhinoconjunctivitis with or without:
    b. Allergic asthma (Global Initiative for Asthma (GINA ≤ Step 3)
3. A valid positive SPT (mean wheal diameter ≥7 mm obtained after screening, duplicate cat dander extract SPT) for cat.
4. Cat specific serum immunoglobulin E (IgE) measured by ImmunoCAP (≥1 kU_A/L).
5. Fel d 1 specific serum IgE measured by ImmunoCAP (≥1 kU_A/L).
6. Female subjects must be:
    a. of non-child-bearing potential [surgically sterilized or post–menopausal (12 months with no menses without alternative medical cause)] OR
    b. not pregnant, non breast feeding or planning to become pregnant AND willing to comply with the highly effective or effective contraceptive requirements of the study from Screening to at least 28 days after the last Investigational Medicinal Product (IMP) administration. Highly effective and effective contraceptive methods include : combined hormonal contraceptives (pills, patch or vaginal ring), copper intrauterine device, tubal ligation, progestogen implant, levonorgestrel intra-uterine releasing system and depot medroxyprogesterone acetate SC or IM injections.
7. Able to speak, read and understand English sufficiently to understand the purposes and risks of the study and to provide written informed consent.
8. Willing, able and available to comply with all study procedures.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. History of current clinically significant gastrointestinal, hepatic, renal, cardiovascular, endocrine, oncological, immunological, neurological, ophthalmological, haematological, respiratory or psychiatric disorder or any other condition, which in the opinion of the investigator or sponsor would jeopardize the safety of the subject or the validity of the study results.

2. Severe or uncontrolled asthma as assessed by the GINA Asthma symptom control questionnaire OR current treatment for asthma at GINA> Step 3 OR screening FEV1 less than 80% predicted.
3. Subjects with a medical history of any previous episode of severe or life-threathening anaphylaxis or anaphylactic shock
4. Subjects with skin disorders that would hinder skin testing and/or its interpretation (e.g., severe generalized active atopic dermatitis).
5. Large tattoo(s) on the forearm, which could prevent the adequate assessment of wheal size, according to the investigator.
6. Any medical condition in which adrenaline (epinephrine) is contraindicated. A valid positive SPT (mean wheal diameter ≥7 mm obtained after screening, duplicate cat dander extract SPT) for cat.
7. Female subjects must be:
    a. of non-child-bearing potential [surgically sterilized or post–menopausal (12 months with no menses without alternative medical cause)] OR

    b. not pregnant, non breast feeding or planning to become pregnant AND willing to comply with the highly effective or effective contraceptive requirements of the study from Screening to at least 28 days after the last Investigational Medicinal Product (IMP) administration. Highly effective and effective contraceptive methods include : combined hormonal contraceptives (pills, patch or vaginal ring), copper intrauterine device, tubal ligation, progestogen implant, levonorgestrel intra-uterine releasing system and depot medroxyprogesterone acetate SC or IM injections

8. Currently using or using within the specified timeframe of any of the list of prohibited drugs provided in this protocol.

Investigational medicinal product :

ANG101 will be supplied as a sterile suspension of 33 µg/mL Fel d 1 in PBS at pH 7.4

Reference product:

The ALK commercial cat dander extract (cat Soluprick 100,000 SQ) content of Fel d 1 of the lot to be used is 41 ug/ml. The lot to be used was assayed for Fel d 1 concentration prior to the study using an immunoblot test, in order to adjust the vaccine dilution factors. Sterile Sodium Chloride Injection BP 0.9% w/v will be used as well as the diluent.

Duration of Phase 0 :

14-35 days from screening to the end of safety follow-up, for each subject

Patient withdrawal and study stopping rules:

1. **Individual patient stopping rules:**
    - Occurrence of at least 1 CTCAE grade 3 or 4 systemic adverse event of an at least *possible* causal relationship with at least one of the tested products 1 treatment emergent Serious Adverse Event (TESAE) of an at least *possible* causal relationship

2. Trial stopping rules

- Occurrence of a single Serious Adverse Reaction (SAR), regardless of type.
- Ocurrence of 2 Severe Adverse Drug Reactions (ADRs), regardless of type**.**

Statistical methods:

Sample size:

The study is exploratory as there is no preexisting data on which to base a power calculation. The study size (N=20) is based on a previous study where n=15-17 subjects was sufficient to detect a greater than 1 1⁄2 log (30-fold shift) to the right in the provocation concentration of allergen to cause a ≥ 5 mm skin wheal after subcutaneous grass pollen immunotherapy. Empirically a minimum of a 10-fold shift will be regarded as the minimal clinical important difference (MCID) and/or a reduction in mean plateau wheal diameter of ≥ 50%. comparisons of the plateau reaction among all 3 groups. The sizes of the intradermal skin early phase response (EPR) and LPR will also be compared according to the same hierarchy.

Sentinel dosing will be performed in 3 participants to assess the dose-response and wheal sizes prior to performing Day 1 procedures in the remaining subjects.

A summary of the number and percentage of subjects with adverse events will be prepared, including adverse events by intensity, adverse events by relationship to Fel d 1-eBP, and serious adverse events. Adverse events will be coded using the MedDRA dictionary.

Vital signs (body temperature, respiratory rate, heart rate, oxygen saturation and blood pressure) will be summarized by timepoint. Changes over time in vital signs from pre-SPT will be summarized.

Physical examination data will be listed only.

The number and percentage of subjects receiving concomitant medications will be tabulated overall and by medication received.

Skin tests:

The primary skin reactivity/efficacy outcome will be the provocation concentration of allergen that caused a ≥ 5mm skin wheal. The results obtained for ANG101 vs. commercial cat dander extract will be used for the primary analysis. Secondary analyses will include the provocation concentration of allergen that caused a ≥ 3 mm skin wheal, as well as comparisons of the plateau reaction among the 2 groups. The sizes of the intradermal skin early phase response (EPR) and LPR will also be compared according to the same hierarchy. The analysis will be an unpaired test using either the Student T-test or Mann Whitney U-test depending on the distribution of the data being normal or skewed. A—2 degrees of freedom and a two-tailed test will be employed. There will be no correction for multiple comparisons.

3.0 RESULTS

3.1 Patients disposition

A total of 45 adult patients were screened for study eligibility. Among those subjects, 22 were found eligible per the study inclusion and exclusion criteria, while 23 failed screening for various reasons.

Among the 22 eligible patients enrolled in the study, two had to be discontinued i.e one because of inability to undergo the IDT tests (subject 005) and a second one because of an AE (subject 24). Twenty patients completed the study in full compliance with the protocol.

The screen fail rate was about 50 %, a prevalence originally expected by the clinical investigators.

The mean age of subjects who completed all study procedures was 30.41 years old, 64 % were white Caucasian, and 68 % of enrolled patient were women.

SCREENED	**45**
SCREEN FAILURE	**23**
COMPLETED THE STUDY	**20**
WITHDRAWN	**2**

3.2 Summary of study participants profile: demographics, medical history, adverse event occurrence and concomitant medications

Table 1 list the main information, per subject, for demographics, medical history, adverse event occurrence and concomitant medications

Table 1: Patients demographics, medical history, and concomitant medications (N: 22, includes the 2 subjects withdrawn post enrolment)

Patient ID	Sex-age-race	FEV-1	Asthma	Other allergies	Screening cat dander wheal diameter	Conc. meds
001	M-33-white	95 %	No	Yes (grass pollen, dog)	8.5 mm	Betamethasone topical Gaviscon Mometasone nasal Stopped: diazepam, cetirizine
003	M-24-mixed	78 %	No	Yes (dust mite, grass pollen)	12.5 mm	No
004	F-21-asian	93 %	No	Yes (dust mite, grass pollen)	10 mm	Rigevidon (contraceptive)
005 D/C, could not complete V1 (IDT)	F-25-white other	122 %	No	No	10.5 mm	Nuvaring (contraception)
006	F-29-white	112 %	Yes	Yes (pollen, ferret, rabbit)	8 mm	Microgynon (contraceptive) Flixonase Vitamid D Fostair (asthma) Stopped:fexofenadine
009	F-30-white	102 %	No	Yes (dust mite, pollen, horse)	9 mm	Evra (contraception) Sertraline Stopped: cetirizine
011	F-30-white	109 %	No	Yes (dust mite, feathers, mould spore,grass pollen, penicillin	7.5 mm	Rigevidon (contraceptive) Nifedipine
014	F-33-asian	101 %	No	Yes (grass pollen, dust mite)	9 mm	Milena(contraceptive) Levothyroxine Stopped: fexofenadine
020	F-24-white	118 %	No	Yes (pollen)	8.5 mm	Copper IUD(contraceptive)

						Stopped: Zyrtec
023	M-34-white	100 %	No	Yes (hayfever)	8 mm	Stopped: antihistamins, nasal spray, paracetamol
024 (D/C at V1 because of AE)	F-22-asian	83 %	No	No	7 mm	Evra patch (contraceptive) Stopped: cetirizine
025	F-39-white	103 %	No	Yes (horse, pollen, dust mite)	7 mm	Mercilon(contraceptive) Dymista
029	M-35-white	104 %	Yes	Yes(pollen, dust mite, dog, rabbit)	10 mm	Symbicort, salbutamol, sertraline, Vitamin D Stopped: cetirizine
033	F-37-white	106 %	Yes	Yes (dog, dust mite)	7.5 mm	Ventolin, clenil modulate, Microgynon (contraceptive) Stopped : loratadine
034	M-32-black	80 %	Yes	Yes (dog, dust mite, pollen)	7.5 mm	Clenil modulate Stopped: Pyriton
035	F-59-white	104 %		Yes (pollen, dust mite)	11.4 mm	None
036	F-27-white	88 %	Yes	Yes (birch pollen, dog, brazil nut, grass pollen	9.5 mm	Salbutamol, clenil modulate, copper IUD (contraceptive)
037	F-25-white	93 %	No	Yes (dog, horse, rabbit, pollen)	7 mm	Desogestrel, lycoperen, astaxanthin
038	F-30-mixed white asian	113 %	No	Yes (hayfever, dust mite, horse)	8.5 mm	IUD (contraceptive) Stopped: fexofenadine
039	M-22-white	113 %	No	No	8.8 mm	Multivitamin Stopped: antihistamine
041	M-30-white	106 %	Yes	No	7.25 mm	Foster Stopped: loratadine

044	F-28-mixed white asian	97 %	Yes	Yes (hayfever, dust mite, dog)	7.75 mm	Salbutamol, Nexplanon (contraceptive) Stopped: fexofenadine
Mean +/- SD		100.9 mm +/- 11.8 mm			8.3 mm +/- 1.3 mm	
N: 22 enrolled N: 20 complete	15/22 F (68 % F) 14/22 White (64 %) Age: 30.41 +/- 8.09		7/22 asthma (32 %)	18/22 other allergies (81 %)		

As shown in this table, the majority of enrolled subjects were female and of a Caucasian origin. Only 32 % were asthmatic, in addition of suffering from conjunctivitis or rhino-conjunctivitis, and the majority had allergies other than cat dander, grass pollen and dust mite being the most prevalent concomitant allergic conditions.

Other prior and current conditions included mild gastrointestinal ailments, anxiety disorders and skin conditions. Most eligible patients were allergic to allergens other than cat dander. Dog hair, grass pollen, birch and house dust mite represented highly prevalent concomitant allergies.

Moreover, cat dander skin wheal diameter measured at screening in eligible patients is shown in Table 2:

Table 2: Screening post cat dander SPT skin wheal diameters

	First Cat dander	**Second Cat dander**	**Mean**
N	20	20	20
Mean	8.90	8.48	8.69
SD	1.74	1.52	1.44

3.3 Screen failures

Table 3 lists all cases of screen failures (N: 23), with their reported cause.

Table 3: Screen failures and their reason

Patient ID	Related INC or EXC number	Reason
002	Exc. no 8	Use of prohibited medication
007	Inc. no 4	Cat specific IgE threshold not met
008	Exc. no 14	Clinically significant abnormality
010	Inc. no 3	Cat dander SPT wheal size less than 7 mm
012	Inc. no 3	Cat dander SPT wheal size less than 7 mm
013	Inc. no 3 and 5	Cat dander SPT wheal size less than 7 mm and Fel d 1 specific IgE threshold not met
015	Inc. no 3	Cat dander SPT wheal size less than 7 mm
016	Inc. no 4 and 5	Cat specific and Fel d 1 specific IgE thresholds not met
017	Inc. no 3	Cat dander SPT wheal size less than 7 mm
018	Inc. no 3	Cat dander SPT wheal size less than 7 mm
019	Exc. No 10	Use of immunomodulatory therapy
021	Inc. no 3	Cat dander SPT wheal size less than 7 mm
022	Inc. no 4 and 5	Cat specific and Fel d 1 specific IgE thresholds not met
026	Inc. no 5	Fel d 1 specific IgE thresholds not met
027	Exc. No 8	Use of prohibited medication
028	Exc. No 14	Clinically significant abnormality
030	Inc. no 4 and 5	Cat specific and Fel d 1 specific IgE thresholds not met
031	Exc. No 8	Use of prohibited medication
032	Incl. no 3	Cat dander SPT wheal size less than 7 mm
040	Inc. no 3	Cat dander SPT wheal size less than 7 mm
042	Inc. no 3	Cat dander SPT wheal size less than 7 mm
043	Inc. 4 and 5	Cat specific and Fel d 1 specific IgE thresholds not met

045	Exc. 2	Severe or uncontrolled asthma

3.4 Primary study endpoint: safety

Very few adverse events were reported in the 22 enrolled patients. Three (3) Non-Treatment Emergent Adverse Events (NTEAEs) occurred during screening, in subjects no. 008 (elevated ALT), 027 (use of prohibited drug) and 028 (elevated HCG). On the other hand, a total of eight (8) Treatment Emergent Adverse Events (TEAEs) were reported, in 5 patients. More than 1 event was reported by subject 011 (2 events) and 023 (3 events). One TEAE (patient 024) led to study discontinuation prior to clinic visit 1 (flu like symptoms). All TEAEs were mild, of possible causality with the study tested products (subjects 023 or 029), or unrelated. All events resolved quickly without any sequelae. It is important to mention that the ANG22-01H study was open label and evaluated the safety of two products, namely ANG101 and ALK Soluprick used as an active comparator. Since each enrolled subject received both products at the same time, by the epicutaneous and the intradermal routes, it was almost impossible to differentiate them for AE causality. In this trial, there was no immediate events post-SPT or post-IDT reported. One patient (subject 038, white-Asian female, 33 years old) reported mild chest tightness 8 minutes after the last ID administration of ANG-101 in the elbow. Vital signs were within normal range and were closely monitored without changes. There were no clinical signs of bronchospasm and FEV-1 was unchanged. About 1 hour later the symptoms resolved completely. This event was considered non clinically significant but possibly related to the study IMP and/or its comparator. However, it was not completely unexpected, as a post-IDT event, and was a subjective symptom that could have been entirely non-specific and non-IgE mediated (anxiety etc). Moreover, no treatment was deemed necessary. Finally, there was no Serious Adverse Event or SUSAR reported during the study.

Table 4 provides general safety information on the reported AEs.

Table 4: Description of adverse events which occurred during the study

SUBJECT	TERM	SEVERITY	SERIOUS	RELATIONSHIP TO STUDY DRUG
8	Increased ALT	MODERATE (GRADE 2)	NO	UNRELATED
11	Dizziness	MILD (GRADE 1)	NO	POSSIBLY RELATED
11	Contact Eczema caused by Plaster	MILD (GRADE 1)	NO	UNRELATED
23	Headache	MILD (GRADE 1)	NO	POSSIBLY RELATED
23	Joint pain	MILD (GRADE 1)	NO	POSSIBLY RELATED
23	Tiredness	MILD (GRADE 1)	NO	POSSIBLY RELATED

24	Flu-like Illness	MILD (GRADE 1)	NO	UNRELATED
27	Urticaria	MILD (GRADE 1)	NO	UNRELATED
28	Positive serologic Human Chorionic Gonadotrophin	MILD (GRADE 1)	NO	UNRELATED
29	Cold-like Symptoms	MILD (GRADE 1)	NO	UNRELATED
38	Chest tightness	MILD (GRADE 1)	NO	POSSIBLY RELATED

3.5 Secondary study endpoints

3.5.1 Allergenicity- SPT results

As described in the study protocol, allergenicity of the new ANG101 Fel d 1 BP biological was assessed by performing duplicate Skin Prick Tests (SPTs) with this product, vs an active, commercially available comparator (ALK Soluprick) and measuring the mean induced wheal diameters. Serial dilutions ranging from 1/60,000 to 1/1.2 for ALK and 1/50,000 to undiluted colloidal suspension for ANG101 were tested. A 5 mm minimal, mean wheal diameter was used as the clinically significant threshold. This threshold is a well accepted endpoint for diagnostic SPT, among clinical allergy experts. The product dilutions inducing this minimal skin reaction, expressed as Fel d 1 concentrations, were then reported for both ANG101 and its comparator, allowing the calculation of the allergenicity factor. The same approach was also followed using a 3 mm minimal mean wheal diameter, as an additional and secondary allergenicity endpoint.

Table 5 shows the results obtained, for both mean wheal diameter thresholds. Data are expressed in terms of dilutions and corresponding Fel d 1 concentrations.

Among the 20 patients who had completed the study, only 7 showed a reportable value for the Fel d 1 concentration inducing a 5 mm wheal diameter. In all these subjects, the threshold was reached with the undiluted product. The 5 mm threshold was never reached in the remaining 13 subjects, while all 20 patients reported a Fel d 1 conc. value for it. *Per se*, this significant difference strongly indicates that ANG101 was significantly less allergenic than ALK Soluprick.

Moreover, when a statistical comparison is made between the two products in these 7 patients, using the Student T test (2 independent means, two-tailed, Type I error of 0.05), the difference between the Fel d 1 concentrations inducing a 5 mm minimum mean wheal diameter is $p<0.001$, i.e. highly significant, despite the very small sample size (N: 7, mean ANG101 Fel d 1 conc: 33.0 +/- 0 ug/ml vs mean ALK Soluprick Fel d 1 conc: 0.59 +/- 0.23 ug/ml). In this context, ANG101 was shown to be 55.93 X less allergenic than ALK Soluprick. Since in 13/20 patients the 5 mm threshold could not be reached with ANG101 even at a 33 ug/ml Fel d 1 concentration, we can realistically infer that the allergenicity difference in the whole ANG22-01 study patient sample is in fact much greater than the one reported.

Similar finding were obtained when the 3 mm minimum mean wheal diameter is used as a threshold. In this case, this threshold was reached in 18/20 patients with the ANG101 product, and all patients with ALK Soluprick. Mean Fel d 1 concentration inducing a 3 mm wheal was 16.7 +/- 15.2 ug/ml for ANG101 and 0.77 +/- 1.54 ug/ml for ALK Soluprick, representing a 21.69 X difference in favor of ANG101 ($p<0.001$). However, the 3 mm wheal size was at the limit of sensitivity of the SPT test, which explains why a much greater between patient variability was observed vs the 5 mm one. For example, ALK Soluprick dilutions inducing a 3 mm wheal, varied from 1/6 to 1/6000 (0.066 to 33 ug/ml for ANG101) from one patient to another.

Table 5 : ANG101 and ALK Soluprick dilutions/Fel d 1 conc. inducing a 5 and 3 mm minimum, mean skin wheal diameter post SPT

Patient ID	Dilution-5 mm wheal-ANG101	Fel d 1 concentration (ug/ml)	Dilution-3 mm wheal ANG101	Fel d 1 Conc. (ug/ml)	Dilution-5 mm wheal-ALK	Fel d 1 Conc. (ug/ml)	Dilution-3 mm wheal-ALK	Fel d 1 Conc. (ug/ml)
001	Undiluted	33	Undiluted	33	1/60	0.68	1/60	0.68
003	Not reached		Not reached		1/60	0.68	1/60	0.68
004	Not reached		Undiluted	33	1/6	6.8	1/60	0.68
006	Undiluted	33	1/5	6.6	1/60	0.68	1/600	0.068
009	Not reached		1/50	0.66	1/60	0.68	1/600	0.068
011	Not reached		Undiluted	33	1/60	0.68	1/60	0.68
014	Undiluted	33	1/500	0.066	1/600	0.068	1/6000	0.0068
020	Not reached		Undiluted	33	1/6	6.8	1/60	0.68
023	Not reached		1/50	0.66	1/6	6.8	1/60	0.68
025	Not reached		1/5	6.6	1/6	6.8	1/60	0.68
029	Not reached		Not reached		1/6000	0.0068	1/6000	0.0068
033	Not reached		Undiluted	33	1/6	6.8	1/60	0.68
034	Undiluted	33	1/5	6.6	1/60	0.68	1/6000	0.0068
035	Undiluted	33	Undiluted	33	1/60	0.68	1/600	0.068
036	Not reached		1/5	6.6	1/6	6.8	1/60	0.68
037	Not reached		Undiluted	33	1/6	6.8	1/60	0.68
038	Undiluted	33	1/50	0.66	1/60	0.68	1/6000	0.0068
039	Undiluted	33	1/50	0.66	1/60	0.68	1/600	0.068
041	Not reached		Undiluted	33	1/6	6.8	1/6	6.8
044	Not reached		1/5	6.6	1/6	6.8	1/60	0.68
Mean +/- SD		**N: 7 33.0 +/- 0**		**N: 18 16.7 +/- 15.2**		**N: 7 0.59 +/- 0.23**		**N: 18 0.77 +/- 1.54**

Table 6 and 7 shows the statistical comparison between ANG101 and its comparator, ALK Soluprick, using the Student T test for 2 independent means (alpha error: 0.05, beta error: 0.1)

Table 6: Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Concentration_5_mm_Vaccine	33.00	7	.000	.000
	Concentration_5_mm_ALK	.592571	7	.2313143	.0874286
Pair 2	Concentration_3_mm_Vaccine	16.65033	18	15.226413	3.588900
	Concentration_3_mm_ALK	.771800	18	1.5370040	.3622753

Table 7: Paired Samples Test

		Paired Differences					t	df	Significance	
					95% Confidence Interval of the Difference					
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			One-Sided p	Two-Sided p
Pair 1	Concentration_5_mm_Vaccine - Concentration_5_mm_ALK	32.40	.23	.0874286	32.193498	32.6213586	370.673	6	<.001	<.001
Pair 2	Concentration_3_mm_Vaccine - Concentration_3_mm_ALK	15.87	14.73	3.4737852	8.5494871	23.2075795	4.571	17	<.001	<.001

3.5.2 Intradermal Test (IDT) results

It was proposed to perform an intradermal allergen challenge with ANG101 compared to ALK Soluprick in intradermal challenge after the SPT tests, with monitoring of immediate (15 min) response (Early Phase Response: EPR, for safety and allergenicity) and Late-Phase Response (LPR) at 6.5 Hours (for immunogenicity assessment). The late-phase skin response following intradermal administration of the Fel d 1-BP vaccine was compared to the commercial extract diagnostic challenge test at 6.5 hours after injection. These two measures can provide information on IgE-dependent (early phase) allergenicity and IgE-independent (late phase) immunogenic effects of Fel d 1-eBP. Moreover, the late phase response is indicative of the maintenance of the immunological effects induced by the products injected by the ID route.

A 1/1000 dilution of the provocation concentration of Fel d 1 allergen that caused a 3 mm skin wheal as judged by the previous same-day extinction dilution skin testing was used for both ANG101 and ALK Soluprick—towards the wrist, then after a 30-minute wait period, a 1/100 dilution was administered closer to the elbow. **Table 8** shows the mean wheal diameter obtained 15 minutes after IDT (EPR) and 6.5 hours later (LPR), for both ANG101 and its ALK Soluprick comparator.

Table 8: Post-IDT mean wheal diameter after a low (1/1000 dilution) and a high dose (1/100 dilution) of ANG101 and ALK Soluprick

Table 8: Post IDT Mean Wheal Diameter (EPR and LPR)

	ANG101 High Dose EPR	ALK High Dose EPR	ANG101 Low Dose EPR	ALK Low Dose EPR	ANG101 High Dose LPR	ALK High Dose LPR	ANG101 Low Dose LPR	ALK Low Dose LPR
1	12.00	12.00	6.00	8.00	71.00	69.50	30.00	35.00
2	8.00	10.00	6.00	10.00	66.00	83.00	14.00	24.00
3	14.00	14.00	10.00	14.00	73.00	67.00	32.50	25.50
4	8.00	12.00	7.00	7.00	68.00	86.00	22.00	60.00
5	6.00	7.00	4.00	7.00	72.00	76.00	67.00	69.00
6	9.00	9.00	8.00	9.00	75.00	56.00	43.00	61.00
7	8.00	5.50	5.00	5.50	55.00	96.00	64.00	71.00
8	7.50	8.00	7.00	7.00	79.50	103.00	84.50	91.50
9	13.00	12.00	9.00	9.00	93.00	138.00	104.00	115.00
10	53.00	54.00	39.00	32.50	78.00	91.00	46.00	53.00
11	10.00	12.00	11.00	11.00	69.00	64.00	60.00	45.00
12	10.00	10.00	8.00	9.00	62.00	47.00	47.00	30.00
13	8.50	9.00	6.00	9.00	46.00	46.50	23.50	25.50
14	12.00	11.00	4.50	8.00	106.00	109.50	89.00	93.50
15	6.00	10.00	7.00	6.00	103.00	91.00	54.00	96.00
16	10.50	9.50	6.50	8.00	102.00	123.00	93.00	81.00
17	9.00	10.00	11.00	9.00	76.00	93.00	10.00	64.00
18	8.00	9.00	9.00	9.00	65.00	177.00	47.00	132.00
19	11.00	9.00	10.00	12.00	87.00	100.00	48.00	87.00
20	9.00	11.00	9.00	10.00	61.00	45.00	22.00	37.00

Mean +/- SD	**11.63 +/- 9.97**	**12.20 +/- 10.03**	**9.15 +/- 7.32**	**10.00 +/- 5.66**	**75.38 +/- 16.00**	**88.10 +/- 32.75**	**50.05 +/- 27.16**	**63.33 +/- 32.17**

There was a statistically significant or almost significant difference between high dose and low dose EPR for both ANG101 (11.63 +/- 9.97 vs 9.15 +/- 7.32, p: .007) and ALK Soluprick (12.20 +/- 10.03 vs 10.00 +/- 5.66, p:

059), respectively. The same observations were made for LPR ($p < 0.001$, Table 9). These results were expected considering the 10X greater Fel d 1 concentration of the dilution used for high vs low dose.

Moreover, when ANG101 and ALK Soluprick are compared in terms of mean wheal size, for both low and high doses of Fel d 1, there is no statistically significant difference reported at EPR. At LPR, however, borderline or significant differences can be seen between the products tested, especially when the low dose is considered (50.05 +/- 27.16 vs 63.33 +/- 32.17, p: .017), as shown in Table 10. These findings suggest that despite the 23 X lower dilution of ANG101 needed to induce a 3 mm wheal size, vs ALK Soluprick, a similar immunological skin reaction occurred at EPR, and was comparable at LPR.

These results indicate that while greater mean wheal dimeters were observed during LPR vs EPR, for both products, comparable values were obtained for ANG101 and ALK Soluprick during both reactions. However, since a mean difference of 23 X in the dilution required to induce a minimum 3 mm mean wheal diameter. ANG101 proved to be, again, significantly less allergenic than ALK Soluprick following intradermal administration of the products, while retaining significant immunogenicity at 6.5 hours post-IDT , as shown by the larger wheals reported during LPR. Moroever, the significant wheal sizes observed at LPR for ANG101 confirmed that despite its demonstrated hypoallergenicity, a significant immunogenic reaction was still present 6.5 hrs post IDT, indicating the maintenance of its immunogenicity.

Table 9: Paired Samples Test, multiple ANG101 and ALK Soluprick comparisons, high dose vs low dose, at EPR and LPR

		Paired Differences					t	df	Significance	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			One-Sided p	Two-Sided p
Pair 1	ANG101 High Dose EPR - ANG101 Low Dose EPR	2.47500	3.63635	.81311	.77314	4.17686	3.044	19	.003	.007
Pair 2	ALK High Dose EPR - ALK Low Dose EPR	2.20000	4.90274	1.09629	-.09455	4.49455	2.007	19	.030	.059
Pair 3	ANG101 High Dose LPR - ANG101 Low Dose LPR	25.35000	21.63580	4.83791	15.22413	35.47587	5.240	19	<.001	<.001
Pair 4	ALK High Dose LPR - ALK Low Dose LPR	23.27500	16.66108	3.72553	15.47738	31.07262	6.247	19	<.001	<.001

Table 10: Paired Samples Test

		Paired Differences					t	df	Significance	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			One-Sided p	Two-Sided p
Pair 1	ANG101 High Dose EPR - ALK High Dose EPR	-.57500	1.70352	.38092	-1.37227	.22227	-1.510	19	.074	.148
Pair 2	ANG101 Low Dose EPR - ALK Low Dose EPR	-.85000	2.39022	.53447	-1.96866	.26866	-1.590	19	.064	.128
Pair 3	ANG101 High Dose LPR - ALK High Dose LPR	-12.70000	29.32145	6.55648	-26.42286	1.02286	-1.937	19	.034	.068
Pair 4	ANG101 Low Dose LPR - ALK Low Dose LPR	-14.77500	25.32030	5.66179	-26.62527	-2.92473	-2.610	19	.009	.017

4.0 BAT and DAO tests results

The Basophil Activation Test as well as the Diamine Oxydase Test were performed by Professor Mohamed Shamji, from the Immunomodulation and Tolerance Group, Imperial College London, London, UK.

Method

Whole blood was obtained from 21 eligible and well-characterised cat allergics (CA) with positive skin prick test (≥7 mm), cat specific IgE (sIgE) to Fel d 1 (≥1 kU_A/L) and Fel d 1-sIgE (≥1 kU_A/L). The capacity of Fel d 1 BP and native Fel d 1 to elicit basophil activation, and histamine release was measured by flow cytometry. In brief, whole blood were incubated with increasing concentration of cat allergen extract (ALK Soluprick) or ANG101 (0, 1, 3, 10, 33 and 100 ng/mL) for 15 minutes at 37°C in the presence of flurochrome-conjugated antibodies (CD3, CD294, CD303, CD63 and CD203c). Red blood cells were lysed using BD Cell Lysis solution for 10 minutes in the dark followed by washing at 400 g for 5 minutes. Cells were fixed and permeabilised using BD Cell Fix/Perm for 20 minutes at 4°C and stained intracellularly with diamine oxidase (DAO) for 30 minutes at 4°C. Cells were resuspended in wash buffer prior to acquisition on the BD FACS Canto II. Data analysis was performed using FlowJo software.

Results

Cat allergen extract (ALK Soluprick) elicited a dose-dependent increase in basophil activation ($CD63^+CRTh2^+$ and $CD203c^{bright}CRTh2^+$) and histamine release ($DAO^-CD63^+CRTh2^+$ and $DAO^-CD203c^{bright}CRTh2^+$; Figure 3A-B) with peak maximal response observed at 10ng/mL ($CD63^+CRTh2^+$= 54.20±6.99% and $DAO^-CD63^+CRTh2^+$= 30.39±6.31%; Figure 2C-D). Fel d 1-eBP induced a rightward shift in the dose-response curve with a peak maximal response observed at 100ng/mL ($CD63^+CRTh2^+$= 24.18±6.97% and $DAO^-CD63^+CRTh2^+$= 13.07±5.27%). Moreover, the hypo-allergenic nature of Fel d 1-eBP is evident from a reduced area under the curve (AUC) for all markers investigated, compared to cat allergen extract (3.93-fold for $CD63^+CRTh2^+$, 3.96-fold for $CD203c^{bright}CRTh2^+$, 4.90-fold for $DAO^-CD63^+CRTh2^+$ and 4.45-fold for $DAO^-CD203c^{bright}CRTh2^+$; all, P<0.001) (Figure 4A-D).

Table 18: BAT and DAO ANG101 and cat dander extract (ALK Soluprick) % CD63 + and CD203bright basophils

		[Phl p] (ng/mL)					
		0	1	3	10	33	100
ANG101 %CD63 + Basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	2.04	3.27	8.18	9.26	19.75	23.96
	95.0% Lower CL for Mean	2.00	1.37	-.15	-.13	7.33	9.31
	Standard Deviation	.09	4.07	17.29	20.06	26.53	31.31
	95.0% Upper CL for Mean	2.08	5.17	16.52	18.65	32.17	38.62
	Median	2.04	2.10	2.49	2.23	4.14	3.54
Cat Extract %CD63 + Basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	2.04	30.96	46.28	52.26	54.39	52.65
	95.0% Lower CL for Mean	2.00	16.99	31.36	36.65	40.49	40.07
	Standard Deviation	.09	29.85	31.87	33.36	29.71	26.88
	95.0% Upper CL for Mean	2.08	44.93	61.19	67.87	68.30	65.23
	Median	2.04	14.30	56.00	66.05	66.40	63.00
ANG101 %CD203cbright Basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	2.01	3.48	8.39	10.39	23.00	24.99
	95.0% Lower CL for Mean	1.97	1.41	.02	1.15	10.12	10.52
	Standard Deviation	.09	4.41	17.36	19.76	27.53	30.91
	95.0% Upper CL for Mean	2.05	5.54	16.76	19.64	35.89	39.46

		[Phl p] (ng/mL)					
		0	1	3	10	33	100
	Median	2.03	1.99	2.88	2.80	6.55	7.15
Cat extract %CD203cbright Basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	2.01	31.96	48.06	53.06	56.85	55.51
	95.0% Lower CL for Mean	1.97	18.57	35.14	39.74	45.06	43.78
	Standard Deviation	.09	28.62	27.61	28.47	25.19	25.05
	95.0% Upper CL for Mean	2.05	45.36	60.99	66.39	68.64	67.23
	Median	2.03	16.70	53.45	60.45	66.25	62.25
ANG101 % DAO-CD63+ basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	.16	.16	1.79	3.69	10.03	13.72
	95.0% Lower CL for Mean	.09	.07	-.97	-1.57	.50	2.23
	Standard Deviation	.16	.18	5.72	11.25	20.36	24.56
	95.0% Upper CL for Mean	.24	.25	4.54	8.96	19.56	25.22
	Median	.14	.11	.14	.12	.29	.30
Cat extract CD203 % DAO-CD63+ basophils	Adjusted Total N	20	20	20	20	20	20
	Mean	.16	17.07	26.51	31.91	26.18	18.30
	95.0% Lower CL for Mean	.09	5.73	13.71	18.43	15.37	10.34
	Standard Deviation	.16	24.23	27.35	28.81	23.09	16.99
	95.0% Upper CL for Mean	.24	28.41	39.31	45.40	36.98	26.25
	Median	.14	1.02	16.70	30.05	21.10	15.80
ANG101 DAO- CD203c bright	Adjusted Total N	20	20	20	20	20	20
	Mean	.14	.09	1.64	3.59	9.53	13.17
	95.0% Lower CL for Mean	.07	.04	-.95	-1.57	.20	2.02
	Standard Deviation	.15	.13	5.37	11.01	19.94	23.82
	95.0% Upper CL for Mean	.20	.15	4.23	8.74	18.86	24.31
	Median	.12	.05	.07	.07	.09	.34
Cat extract DAO-CD203c bright	Adjusted Total N	20	20	20	20	20	20
	Mean	.14	14.63	23.47	27.64	22.03	15.68
	95.0% Lower CL for Mean	.07	4.44	11.85	15.24	12.14	8.11

		[Phl p] (ng/mL)					
		0	1	3	10	33	100
	Standard Deviation	.15	21.78	24.83	26.50	21.13	16.18
	95.0% Upper CL for Mean	.20	24.82	35.09	40.05	31.92	23.25
	Median	.12	.92	16.55	22.25	17.45	9.85

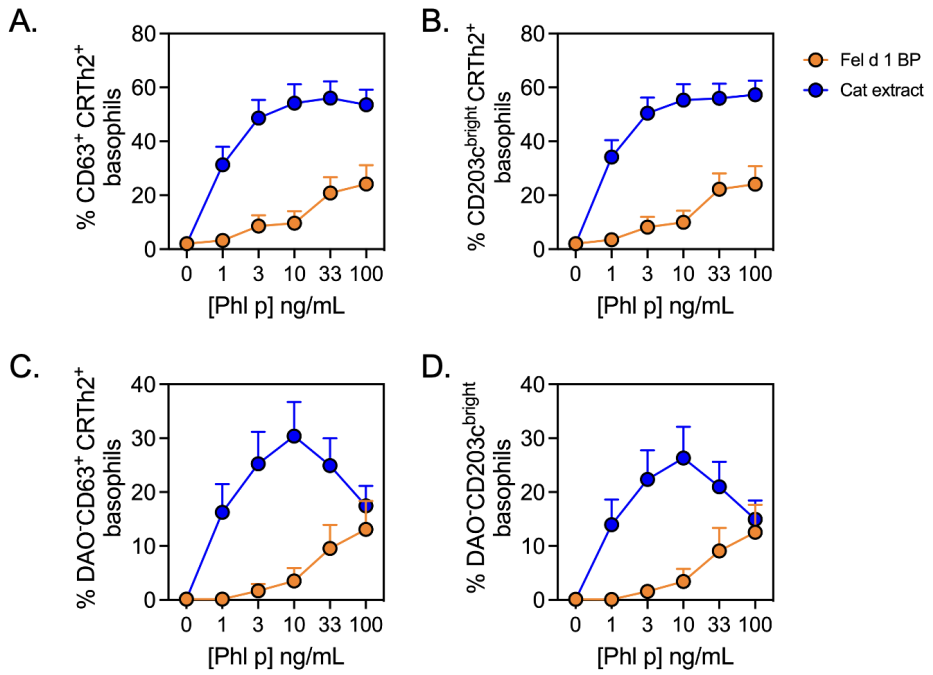

Figure 3. Evaluation of ANG101 (Fel d 1 BP) to elicit basophil activation and histamine release. The ability of cat extract (ALK Soluprick) and ANG101 to elicit basophil activation was assessed through the enumeration of A) $CD63^{+}CRTh2^{+}$ and B) $CD203c^{bright}CRTh2^{+}$ basophils, and histamine release through the enumeration of C) $DAO^{-}CD63^{+}$ $CRTh2^{+}$ and D) $DAO^{-}CD203c^{bright}$ $CRTh2^{+}$ basophils.

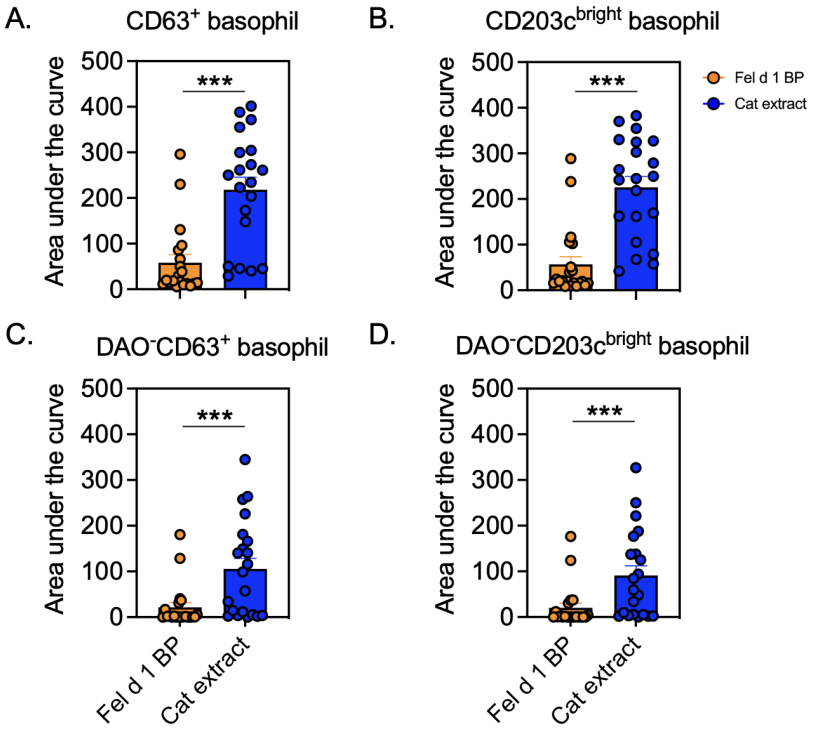

Figure 4. Evaluation of ANG101 (Fel d 1 BP) on area under the curve (AUC) of basophil response. The ability of cat extract (ALK Soluprick) and ANG101 (Fel d 1 eBP) to elicit basophil activation was assessed through the quantification area under the curve for: A) $CD63^{+}CRTh2^{+}$, B) $CD203c^{bright}CRTh2^{+}$, C) $DAO^{-}CD63^{+}$ $CRTh2^{+}$ and D) $DAO^{-}CD203c^{bright}$ $CRTh2^{+}$ basophils. Data presented as mean±SEM. Wilcoxon paired test where *** indicates $P<0.001$.

5.0 DISCUSSION AND CONCLUSION

In this study conducted in adult, well defined cat allergic patients, ANG101 proved to be safe and significantly hypoallergenic. While the open label and concomitant use of the active ALK Soluprick cat dander solution made the interpretation of the safety data more challenging, in terms of causality assessment, the safety profile was overall reassuring, with no SAE (no anaphylaxis or other), and the occurrence of only few mild, fully reversible AEs. A total of 8 Treatment Emergent Adverse Events (TEAEs) were reported, in 5 patients, with more than1 event reported by subject 011 (2 events) and 023 (3 events). One TEAE (patient 024) led to study discontinuation prior to clinic visit 1 (flu like symptoms). Possible causality with the study tested products (ANG101 or ALK Soluprick, or both…) was suggested by the clinical investigator in only 2 subjects (023 or 029).

On the other hand, ANG101 was shown to be significantly hypoallergenic when compared to ALK Soluprick, both following SPT and IDT. First of all, a 5 mm minimum wheal developed in only 7 patients out of 20, while it did in all subjects for the ALK Soluptick. Moreover, among these 7 subjects, a Fel d 1 concentration 56 X higher was required with ANG101 to induce the 5 mm skin wheal threshold, considered clinically significant ($p<0.001$). These results suggest that the true allergenicity difference between ANG101 and ALK Soluprick may even be greater than the one that could be calculated in the small 7 patients subset.

Similar results were found when the IDT findings are considered. While there was a clear demonstration that the skin wheal size was greater at 6.5 hours post IDT (LPR) vs EPR, for both products, comparable values were obtained at both EPR and LPR between the two tested products, despite a 23 X difference in the Fel d 1 exposure at both low and high doses. Moroever, ANG101 immunogenicity was maintained at 6.5 hours post IDT.

Finally, ANG101 was shown to be hypo-allergenic and has reduced capacity to elicit basophil activation and histamine release compared to a cat allergen extract in the BAT and DAO tests.

As a general conclusion, ANG101 was shown to be safe and significantly hypoallergenic in well defined adult cat allergic patients, following epicutaneous and intradermal administration.

In light of these positive results, further clinical development of ANG101 is warranted.

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