Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects

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Summary

**Background** Cat-PAD, the first in a new class of synthetic peptide immuno-regulatory epitopes (SPIREs), was shown to significantly improve rhinoconjunctivitis symptoms in subjects with cat allergy up to 1 year after the start of a short course of treatment.

**Objective** To evaluate the long-term effects of Cat-PAD on rhinoconjunctivitis symptoms following standardized allergen challenge 2 years after treatment.

**Methods** In a randomized, double-blind, placebo-controlled, parallel group study, subjects were exposed to cat allergen in an environmental exposure chamber (EEC) before and after treatment with two regimens of Cat-PAD (either eight doses of 3 nmol or four doses of 6 nmol) given intradermally over a 3-month period. In this follow-up study, changes from baseline in rhinoconjunctivitis symptoms were reassessed 2 years after the start of treatment.

**Results** The primary endpoint showed a mean reduction in total rhinoconjunctivitis symptom scores of 3.85 units in the 4 × 6 nmol Cat-PAD group compared to placebo 2 years after the start of treatment (\(P = 0.13\)), and this difference was statistically significant in the secondary endpoint at the end of day 4 when the cumulative allergen challenge was greatest (\(P = 0.02\)). Consistent reductions in nasal symptoms of between 2 and 3 units were observed for 4 × 6 nmol Cat-PAD compared to placebo between the 2 and 3 h time points on days 1–4 of EEC challenge at 2 years (\(P < 0.05\)). The 8 × 3 nmol dose did not show a meaningful effect in this study.

**Conclusion and Clinical Relevance** A persistent, clinically meaningful reduction in rhinoconjunctivitis symptoms was observed on EEC challenge 2 years after the start of a short course of treatment with 4 × 6 nmol Cat-PAD. This study is the first to provide evidence of a long-term therapeutic effect with this new class of SPIREs.

**Keywords** allergic rhinitis, allergic rhinoconjunctivitis, cat allergy, Fel d 1, immune tolerance, immunotherapy, persistence, SPIREs, T-cell epitopes

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Introduction

Allergy to cat dander results in significant morbidity, with clinical symptoms of allergic rhinoconjunctivitis and, in some cases, asthma [1]. Approximately 17% of the US and 8% of the EU populations display positive skin prick tests to cat allergen [2]. The major cat allergen, Fel d 1, is present ubiquitously in public places at concentrations that are capable of evoking rhinoconjunctivitis and airway symptoms in susceptible individuals [3].

Cat-PAD [also known as ToleroMune\(^\circ\) Cat (Circassia Limited, Oxford, UK)] is the first in a new class of synthetic peptide immuno-regulatory epitopes (SPIREs). It comprises a set of seven synthetic peptide T-cell epitopes whose sequences are derived from Fel d 1 [4]. The proliferative and cytokine responses of peripheral blood mononuclear cells (PBMC) to these seven peptides combined were equivalent to those observed with whole cat dander extract. Unlike whole cat dander extract, however, the seven peptides did not induce significant histamine release in blood basophils. Delivery of T-cell epitopes intradermally is thought to lead to the induction of interleukin-10 (IL-10) and T cells with a regulatory phenotype, which results in downregulation of the response to antigen [5].
Disease-modifying treatment approaches for allergic rhinoconjunctivitis are clinically effective, but can be associated with frequent allergic side effects leading to the requirement for dosing over 3–5 years with multiple visits to the treating physician in the case of subcutaneous immunotherapy (SCIT), and daily dosing in the case of sublingual immunotherapy (SLIT). These protracted, cumbersome treatment regimens result in poor compliance with a recent real world study showing only 23% of subjects completing a 3-year course of SCIT and 7% completing a 3-year course of SLIT [6]. Provision of a safe and rapid alternative to traditional SCIT, displaying equivalent or improved efficacy and prolonged duration of effect will benefit patients, treating physicians and payers alike and may enable patients to be treated who would not otherwise have received immunotherapy.

The importance of immunotherapy over symptomatic therapy is that it may evoke long-term benefits on allergy symptoms and can be potentially curative. While a number of studies have demonstrated long-term effects 2–3 years after cessation of both SCIT and SLIT, all have required treatment over 2–3 years to achieve this benefit [7–11]. We have previously reported that the reduction in rhinoconjunctivitis symptoms following a short course of treatment with a 4 × 6 nmol dose of Cat-PAD (four doses over 12 weeks, with each dose separated by 4 weeks) persisted for 1 year after the start of treatment [12]. The purpose of this follow on study was to evaluate the persistence of the treatment effect of Cat-PAD, 2 years after the start of this single course of treatment (approximately 21 months after the last dosing visit).

Methods

Study design

This was a follow on study at 2 years to a previously completed, randomized, double-blind, placebo-controlled, parallel-group study. In the parent study, the primary assessment of efficacy was 18–22 weeks after the start of treatment; patients were then invited to attend for a further follow-up evaluation at 1 year [12]. A figure summarizing the study design is presented in the Supporting Information. Both the initial parent study and the follow-up evaluations at 1 and 2 years were conducted at the Cetero Research EEC in Mississauga, ON, Canada.

Subjects attended a screening visit, then a baseline challenge of 4 consecutive days of 3-h allergen exposures in the EEC, which occurred before first administration of study medication. In the parent study, 202 subjects were randomized to one of three treatment regimens [eight intradermal doses of Cat-PAD 3 nmol 2 weeks apart (8 × 3 nmol); four intradermal doses of Cat-PAD 6 nmol 4 weeks apart with infill placebo to maintain blinding (4 × 6 nmol); or eight intradermal doses of placebo]. Further details of the dosing regimens and treatment administration are presented in the Supporting Information. After dosing, subjects returned to the EEC for a further 4 consecutive days of 3-h allergen exposures 18–22 weeks after the start of treatment. Eighty-nine subjects were re-enrolled and returned to the EEC for a further 4 consecutive days of 3-h allergen exposures at 1 year (50–54 weeks) after the start of treatment.

In this study, 51 of the 86 subjects, who completed the 1-year follow-up re-enrolled, were screened and returned to the EEC for a further 4 consecutive days of 3-h allergen exposures at 2 years (102–106 weeks) after the start of treatment. A follow-up safety assessment was performed 3–10 days after the final day of EEC challenge. No further treatment with Cat-PAD or placebo was administered between the initial course of treatment in the parent study and the 2-year follow-up. Subjects and study staff remained blinded to treatment throughout. Measures taken to maintain blinding in the follow-up studies included appointment of a new investigator at the clinical site, use of new subject numbers and not informing subjects of their original treatment allocation. The EEC was designed with clean-room technology using 100% fresh high-efficiency particulate air filtering. At each chamber evaluation, cat allergen was dispersed into the EEC by an aerosol generator to achieve consistent mean airborne concentrations of approximately 50 ng Fel d 1/m3 using a fully validated method (Cetero Research). This level of allergen is consistent with levels found in homes that keep a cat [13]. As far as possible, each participant was subjected to challenge at a time of day matched to the time they had completed previous EEC challenges earlier in the study (e.g. always in the morning) to minimize the impact of circadian variations.

The study received prior ethical approval from IRB Services (Aurora, ON, Canada) and from Health Canada’s Biologics and Genetic Therapies Directorate (the Canadian federal authority that regulates biological drugs). It was conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT01604018).

Subjects

Cat allergic subjects aged 18–65 years who had been randomized in the initial study and completed all visits in the 1-year follow on study (n = 86) were contacted regarding their willingness to participate in the further follow on study and asked to attend a screening visit. Those willing to participate (n = 51) attended the
screening visit and provided written informed consent; there were no screen failures, and all 51 subjects were included in this 2-year follow on study. No information was available for the 35 subjects who were not willing to participate in this 2-year follow on study, with respect to the reasons for their non-participation. Subjects with persistent asthma or subjects using inhaled corticosteroids or leukotriene receptor antagonists to manage their asthma were excluded in the original study. Further details are provided in the Supporting Information.

Analysis populations

All subjects enrolled into this 2-year follow on study were included in the intent-to-treat (ITT) and safety populations (see Supporting Information).

Primary efficacy measurement

The primary efficacy measurement was based on total rhinoconjunctivitis symptom score (TRSS). At all EEC visits, subjects recorded symptoms in a diary just before entering the chamber and at 30-min intervals thereafter. Symptoms were divided into: nasal symptoms (running nose, sneezing, blocked nose, itchy nose) and ocular symptoms (itchy eyes, watery eyes, red eyes, sore eyes). For each symptom, the subject rated the severity as: 0 – absent, 1 – mild, barely noticeable, 2 – moderate, annoying/bothersome, 3 – severe, very annoying/very bothersome. TRSS was calculated by summing the nasal and ocular symptom scores at each time point in the EEC. Subjects were required to have had a TRSS of at least 10 of 24 and a total nasal symptom score (TNSS) of at least 6 of 12 on at least one diary card on days 3 and 4 of the baseline challenge in the parent study. The protocol-specified primary endpoint was the mean change in TRSS from 1 h onwards on days 2–4 of the EEC challenge at 2 years compared to the same time points in the baseline challenge.

Secondary efficacy measurements

Pre-specified secondary endpoints included the difference in absolute TRSS at all time points on day 4 of EEC challenge and the mean change from baseline in scores for nasal and ocular components of the TRSS score at time points after 1 h on days 2–4 of EEC challenge at 2 years in each Cat-PAD treatment group compared to placebo.

Safety measurements

Safety parameters at the 2-year follow-up were adverse events (AEs), physical examination, vital signs and forced expiratory volume in 1 s (FEV₁).

Statistical analysis

A comparison of each Cat-PAD dose with placebo was made using an analysis of variance (ANOVA). For the analysis of TRSS at each time point of EEC challenge on day 4, a repeated measures ANOVA mixed model was used. Following sight of the results of the analysis of mean change in TRSS at all time points on day 4 of the challenge, this analysis was extended to include TRSS, TNSS and total ocular symptom scores (TOSS) at all time points on all 4 days of the EEC challenge. In all cases, statistical significance was accepted for $P < 0.05$. Missing data were not replaced.

Results

Study participants

The 86 subjects who completed all visits at 1-year follow-up were invited to participate in this 2-year follow on study. Of these, 51 subjects agreed to participate and attended at least one EEC visit 2 years after the start of Cat-PAD treatment. Details of subject demographics and baseline characteristics are presented in Table 1. Disposition of subjects and numbers analysed are presented in the Supporting Information. Two subjects, 1 each in the 8 nmol and 4 × 6 nmol Cat-PAD groups, were withdrawn from the study due to an FEV₁ < 70% of predicted prior to EEC challenge on day 3 and day 2, respectively. The subject withdrawn from the 4 × 6 nmol group meant that the ITT population (n = 12) for the primary and secondary analyses was effectively reduced to n = 11, as the withdrawn subject had no data for the protocol specified primary endpoint on days 2–4 of EEC challenge.

The mean concentration of Fel d 1 antigen during the 2-year EEC challenge was approximately 50 ng/m³, which was comparable to the exposure in the earlier chamber assessments. The results presented below at all assessment points (baseline, 18–22 weeks, 1 year and 2 years) are for the 2-year study population (n = 51) only, to ensure a valid comparison of the data in this population at the different time points.

Total rhinoconjunctivitis symptom scores

A greater improvement in TRSS between baseline challenge and EEC challenge at 2 years was observed for the 4 × 6 nmol Cat-PAD group compared to placebo (Fig. 1). The 4 × 6 nmol dose showed a mean treatment effect on TRSS of approximately 5 units more than placebo at the end of day 4 of EEC challenge. Improvements from baseline in the 8 × 3 nmol group were not markedly different from placebo.
A summary of the change from baseline in mean TRSS at 1–3 h on days 2–4 (primary outcome) at all time points after the start of treatment for the subjects participating in the 2-year follow on study can be found in Table 2. A sustained decrease in mean TRSS from baseline for 4.96 nmol Cat-PAD (1/C0 5.87) was observed when compared to both 8.93 nmol (1/C0 3.05) and placebo (1/C0 2.02) at EEC challenge 2 years after the start of treatment. The LS mean treatment difference for 4.96 nmol vs. placebo was 3.85 (95% CI 8.83, 1.14; *P* = 0.13).

Figure 2 shows the mean TRSS at each time point on each day for the four EEC visits at baseline challenge and at 1 year and 2 years after the start of treatment. A similar reduction in rhinoconjunctivitis symptoms was observed for 4.96 nmol Cat-PAD after 1 and 2 years. On day 4 of the EEC challenge, TRSS decreased from approximately 16 at the end of the baseline challenge to <10 at the 2 year evaluation for subjects in the 4 × 6 nmol Cat-PAD group. This difference in absolute TRSS at the end of day 4 of the challenge, which was a pre-specified secondary endpoint, was statistically significantly different compared to placebo (LS means 9.00 vs. 14.10, *P* = 0.02).

**Nasal and ocular symptom scores**

Nasal symptom scores were lower on all 4 days of the 2-year EEC evaluation in the 4 × 6 nmol treatment group than in the placebo or 8 × 3 nmol treatment groups (Fig. 3). These lower scores across all 4 days are reflected in a greater mean reduction in TNSS from baseline in the 4 × 6 nmol group (−3.08) than in the placebo (−0.85) or 8 × 3 nmol (−1.39) groups (Table 2). The difference between the 4 × 6 nmol group and placebo showed a trend towards statistical significance (*P* = 0.07).

A similar effect was seen on TOSS (Table 2), although the magnitude of the reduction was somewhat less in the 4 × 6 nmol group (−2.79), whereas in the placebo group it was greater than the reduction in TNSS (−1.17).

The analysis of absolute TNSS at each time point on days 1–4 at EEC challenge 2 years after the start of treatment found significant reductions in TNSS of between 2 and 3 units for 4 × 6 nmol Cat-PAD compared to placebo (*P* < 0.05), particularly between the 2 to 3 h time points (Fig. 4). No significant changes in TOSS were observed at any time point on days 1–4.

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**Table 1. Subject demographics and baseline characteristics**

| Age in years, mean (SD) | Placebo (n = 22) | 8 × 3 nmol (n = 17) | 4 × 6 nmol (n = 12) |
|-------------------------|------------------|---------------------|---------------------|
| Male/Female             | 41.8 (11.1)      | 41.7 (10.8)         | 38.5 (8.8)          |
| Race white, n (%)       | 15 (68.2)        | 12 (70.6)           | 7 (58.3)            |
| Cat-specific IgE (kUA/L), mean (SD) | 9.38 (14.61) | 21.76 (42.69) | 5.70 (6.47) |
| Skin prick size to cat dander (mm), mean (SD) | 10.1 (4.2) | 11.4 (5.1) | 9.7 (6.2) |
| Subjects with a cat at home, n (%) | 7 (31.8) | 2 (11.8) | 5 (41.7) |
| Subjects with asthma, n (%) | 4 (18.2) | 2 (11.8)* | 1 (8.3)* |
| TRSS at baseline, mean (SD) | 15.02 (4.64) | 16.18 (4.21) | 15.30 (3.69)* |

*‡TRSS calculated at 1–3 h on days 2–4 of baseline challenge.

**Fig. 1. Difference in TRSS (means ± SEMs) at each 30-min time point (3 h/day) in the chamber over 4 consecutive days; score at baseline challenge minus score at EEC challenge 2 years after start of treatment. Data censored at Y = 0.**

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Treatment

Five subjects in bronchospasm during EEC challenge accompanied by four AEs. The most commonly reported AE was spasm, followed by an upper respiratory tract infection

There were no serious AEs in this 2 year follow-up study. One subject in the placebo group had broncho-

Table 2. Summary of change from baseline in TRSS, TNSS and TOSS at 1–3 h on days 2–4 after EEC challenge at 18–22 weeks, 1 and 2 years

| Treatment   | n  | 18–22 weeks | 1 year | 2 years | P-value* |
|-------------|----|-------------|--------|---------|---------|
| TRSS        |    |             |        |         |         |
| Placebo     | 22 | – 3.81 (4.69)| – 2.99 (5.64)| – 2.02 (5.66)| –       |
| 8 × 3 nmol  | 17 | – 5.15 (6.25)| – 3.77 (5.89)| – 3.05 (5.84)| 0.64    |
| 4 × 6 nmol  | 11*| – 6.38 (6.78)| – 7.15 (7.74)| – 5.87 (9.47)| 0.13    |
| TNSS        |    |             |        |         |         |
| Placebo     | 22 | – 1.98 (2.62)| – 1.81 (3.02)| – 0.85 (2.69)| –       |
| 8 × 3 nmol  | 17 | – 2.35 (3.00)| – 2.11 (3.32)| – 1.39 (2.84)| 0.61    |
| 4 × 6 nmol  | 11*| – 3.04 (3.96)| – 3.44 (3.97)| – 3.08 (4.81)| 0.07    |
| TOSS        |    |             |        |         |         |
| Placebo     | 22 | – 1.83 (2.63)| – 1.17 (2.87)| – 1.17 (3.34)| –       |
| 8 × 3 nmol  | 17 | – 2.81 (3.70)| – 1.66 (3.45)| – 1.66 (3.28)| 0.68    |
| 4 × 6 nmol  | 11*| – 3.34 (3.43)| – 3.71 (3.96)| – 2.79 (4.78)| 0.24    |

P-values for comparison of 2-year data for active treatments with placebo. *n = 11 for the 4 × 6 nmol Cat-PAD group, as one subject was withdrawn from the study on day 1 of EEC challenge at 2 years.

Safety

There were no serious AEs in this 2 year follow-up study. One subject in the placebo group had broncho-

The largest number of subjects with AEs occurred in the placebo group (six subjects with nine AEs) and the least in the Cat-PAD 4 × 6 nmol group (two subjects with four AEs). The most commonly reported AE was bronchospasm during EEC challenge accompanied by a reduction in FEV1, which occurred in five subjects in the placebo group, one subject in the 8 × 3 nmol Cat-PAD group and two subjects in the 4 × 6 nmol Cat-PAD group. No AEs were considered by the investigator to be related to treatment. The AEs were all assessed as mild or moderate; there were no severe AEs.

Discussion

The purpose of this follow on study was to evaluate the long-term effects of the intradermal administration of a short course of Cat-PAD on rhinoconjunctivitis symp-

The improvement in rhinoconjunctivitis symptoms was still evident in the 4 × 6 nmol Cat-PAD treatment group compared to placebo 2 years after the start of treatment. The lack of statistical significance between the 4 × 6 nmol Cat-PAD group and placebo for the primary endpoint was likely due to the small number of subjects in the study overall, providing insufficient power to attribute significance to the differences observed. A high degree of confidence that the treatment effect has been maintained can be concluded based on the demonstration of a statistically significant improvement in the pre-specified secondary endpoint at the end of day 4 when the cumulative allergen challenge was greatest and when subjects on the placebo group were experiencing their highest level of symp-

To gain greater confidence in this result, an analysis at each time point of absolute TRSS, TNSS, and TOSS on days 1–4 of EEC challenge was undertaken. Significant reductions in nasal symptoms were observed for 4 × 6 nmol Cat-PAD compared to placebo at multiple time points, particularly between 2 and 3 h on days 1–4 when the symptoms evoked by the airborne cat aller-

The use of an EEC allows exposure to aeroallergens in a highly controlled manner and at pre-established allergen levels known to induce moderate to severe symptoms [14, 15]. The standardized pre- and post-treatment allergen challenges used in this study allowed the reproducible determination of efficacy, including the magnitude and duration of treatment effect. The mean concentration of Fel d 1 of approximately 50 ng/m3 in the in the EEC challenge at 2 years was comparable to the mean concentrations measured in the previous EEC challenges [12] and was within the range of 10–200 ng/m3 reported for airborne Fel d 1 concen-

We have previously reported that the greatest treat-

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non-asthmatic population in the study at 1 year, an ITT population (including asthmatic subjects) was used in the primary and secondary analyses in the present study to seek to address the anticipated loss of power associated with the anticipated reduction in subject numbers.

Fig. 2. TRSS (means ± SEMs) at each 30-min time point (3 h/day) in the EEC over 4 consecutive days; (a) baseline, (b) 1 year after the start of treatment, (c) 2 years after the start of treatment. All data are for the 51 subjects in this 2-year follow on study.

Fig. 3. TNSS (means ± SEMs) at each 30-min time point (3 h/day) in the EEC over 4 consecutive days at 2 years after the start of treatment.
The reduction in rhinoconjunctivitis symptoms seen with the 8 × 3 nmol regimen at 2 years is consistent with that observed at the 18–22 week and 1-year assessments [12] and confirms that this dosing regimen is not as effective as the 4 × 6 nmol regimen. The total dose of Cat-PAD administered (24 nmol) was identical in the 8 × 3 and 4 × 6 nmol regimens. It therefore appears likely that a threshold dose is required for each administration to modulate the immune system in a sustained way.

The treatment effects seen at 1 year in subjects who participated in the 2-year follow on study were similar to those seen for subjects at 1 year in the 1-year follow on study [12], where mean changes in TRSS of −6.78 for the 4 × 6 nmol group, −3.89 for the 8 × 3 nmol group and −2.91 for the placebo group were observed. This demonstrates that the subjects who participated in the 2-year follow on study were representative of the 1-year follow on population.

TRSS is commonly used as an outcome measure in studies evaluating the efficacy of pharmacotherapy and immunotherapy in allergic rhinoconjunctivitis. The observed improvement of 3.9 TRSS units reported at 1 year [12] and the sustained improvement of 3.85 TRSS units at 2 years reported here compare favourably with existing pharmacotherapy and immunotherapy for cat allergy, including whole allergen immunotherapy [16], sublingual drops immunotherapy [17] and treatment with the antihistamine fexofenadine [18]. A recent review [19] has summarized the treatment effects observed in these studies and compared them to the treatment effects reported with Cat-PAD at 1 year and concluded the treatment effects with Cat-PAD are favourable. Moreover, the changes in TRSS reported here were observed after just four administrations of Cat-PAD over 12 weeks and have now shown evidence of persistence 2 years after the start of treatment.

The importance of a persistent treatment effect after a short course of treatment cannot be underestimated. While long-term follow-up studies with SLIT tablets have shown evidence for a treatment effect in a second grass season after cessation of 3 years daily treatment, a recent study in the Netherlands found poor overall real-life compliance to SCIT and SLIT, with only 18% of 6486 patients reaching the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%) [6]. If Cat-PAD results in greater or comparable efficacy to SCIT/SLIT regimens in terms of durability and efficacy, then the four injection regimen of Cat-PAD is likely to be preferable both in terms of patient compliance and in reducing the cost burden of treatment. Furthermore, the persistence of the effect of Cat-PAD after a short course of treatment suggests that the goal of safe, long-term disease modification in a manner acceptable to both patients and clinicians may eventually be attained. Future studies might also be considered that evaluate whether an additional course of treatment with Cat-PAD results in a more substantial or more durable treatment effect.

No safety signals associated with prior administration of Cat-PAD were detected during this 2-year follow on study.

In conclusion, this study provides evidence of a persistent, clinically meaningful reduction in rhinoconjunctivitis symptoms in the 4 × 6 nmol group on EEC challenge 2 years after the start of a very short course of treatment with Cat-PAD, the first in a new class of SPIREs. The persistence of a clinically relevant effect should be evaluated in a larger study, with evaluation also continued for longer than the 2 years measured here to determine the duration of these beneficial effects.

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Conflict of interests

RPH is an employee of Circassia Limited and a Director and Shareholder of Circassia Pharmaceuticals plc. KA is an employee of Adiga Life Sciences (a Circassia group company) and has stock options in Circassia Pharmaceuticals plc. ML is a cofounder of Circassia Limited and Adiga Life Sciences, consultant of Circassia Limited, Shareholder of Circassia Pharmaceuticals plc and has received research support from Adiga Life Sciences. PC and DP declared no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Overall Study Design. Baseline Challenge and EEC Challenges at 18–22 weeks, 1 year and 2 years consisted of 3 h in the EEC exposed to cat allergen on 4 consecutive days.

Figure S2. Disposition of subjects and populations for analysis.

Table S1. Treatment regimens and treatment schedule.