

REVIEW ARTICLE

The allergen challenge chamber: a valuable tool for optimizing the clinical development of pollen immunotherapy

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Abstract

The clinical development of allergen immunotherapy for allergic rhinoconjunctivitis because of pollen is complicated by seasonal, geographical and subject-related variability in allergen exposure. Using an allergen challenge chamber (ACC), a room that enables reproducible challenges with controlled levels of inhalant allergens for several hours, these factors can be controlled. The ACC has often been used to evaluate symptomatic medications but is underexploited in the field of allergen immunotherapy. When used in conjunction with a programme of natural-exposure trials, the ACC enables researchers to (i) facilitate the allergen immunotherapy dose-finding process, (ii) accelerate the transition from Phase I/II to Phase III trials, (iii) characterize the onset and maintenance of action, (iv) avoid the confounding effects of rescue medication, (v) better characterize the baseline or pretreatment characteristics of trial subjects, (vi) perform better-standardized physical and laboratory measurements during an acute challenge, (vii) simplify trial logistics and use smaller numbers of subjects than would be required in equivalent natural-exposure studies and (viii) support (but not replace) Phase III natural-exposure trials for the investigation into long-term and disease-modifying effects. ACC studies can further increase levels of evidence for allergen immunotherapy – the only current therapy potentially capable of modifying the underlying allergic disease.

The current status of allergen immunotherapy

Allergen immunotherapy is used with clinical success in reorienting inappropriate immune responses in allergic patients (1). Historically, allergen immunotherapy first consisted of subcutaneously injected preparations of native or chemically modified allergen extracts in solution or adsorbed on colloidal calcium phosphate or aluminium hydroxide (i.e. subcutaneous immunotherapy, SCIT) (2). Sublingual immunotherapy (SLIT) preparations of aqueous allergen extracts have also been extensively tested in the clinic [essentially in Europe (3)] and have received marketing approval in many countries.

Systematic reviews and meta-analyses have demonstrated the clinical efficacy of grass pollen SCIT and SLIT in seasonal allergic rhinitis in adult subjects (4, 5). There has been some debate as to the efficacy of allergen immunotherapy in paediatric populations. Although the 2005 Cochrane Collaboration

meta-analysis (5) failed to observe efficacy in children, two separate meta-analyses of, respectively, 7 and 10 paediatric SLIT trials in seasonal allergic rhinitis published at around the same time concluded as to a significant reduction in the overall symptom score and in rescue medication use (6, 7). However, a 2008 review by Röder et al. (8) stated that 'there is at present insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis'. Since the publication of the Röder et al.'s review, the efficacy of SLIT in paediatric populations has been demonstrated in two recent large-scale, randomized, double-blind, placebo-controlled trials of tablet formulations (9, 10). Lastly, in terms of safety, SCIT is accompanied by a non-negligible risk of potentially fatal adverse events (4, 11). The SLIT formulations have a good safety profile, with mainly local and transient adverse events (12).

However, all the meta-analyses of allergen immunotherapy products have highlighted significant interstudy heterogeneity in the published clinical trials, regardless of the formulation. This is attributed to factors such as the lack of methodological standardization, different treatment doses (including sub-optimal doses), allergen immunotherapy durations, study populations and allergens studied, variability in environmental allergen exposure (both the duration and level), differing scales (for scoring symptom intensity and rescue medication use), insufficient statistical power and, lastly, spontaneous variability in the severity of the allergic disease.

Several key pharmacodynamic factors in immunotherapy (such as the onset of efficacy, long-term effects and disease-modifying effects) are difficult to define precisely in conventional, natural-exposure clinical trials, because of the above-mentioned sources of variability. In a recent report, Horak et al. (13) used an allergen challenge chamber (ACC) to determine the onset of action of a 5-grass pollen sublingual tablet formulation. This article discusses the benefits of integrating the ACC into clinical development programmes for allergen immunotherapy in general and improving the transition from Phase I/II to Phase III trials in particular.

Sources of heterogeneity in natural-exposure allergen immunotherapy studies

The main sources of variability in clinical trials with natural exposure to aeroallergens are summarized in the following sections.

Allergen exposure

Allergen level determination over time is an important aspect of trial design and is crucial for seasonal, airborne allergens such as pollens, because levels of the latter are generally used to define the time period over which efficacy is assessed. In its 2008 'Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases' (14), the European Medicines Agency (EMA) emphasized that the criteria for defining the pollen season and the pollen peak must be stated. In its 2000 draft Guidance for Industry 'Allergic Rhinitis: Clinical Development Programs for Drug Products' (15), the FDA stated that one of the issues that should be considered in prophylaxis trials for seasonal allergic rhinitis is 'the difficulty in capturing the peak of the allergy season or a time when pollen counts are at their highest'.

By way of an example, the start, peak and end of the Pooideae grass flowering season can vary by up to 8 weeks from one European country to another (16). This variability is illustrated in Fig. 1, which compares pollen counts in Paris (France) and Copenhagen (Denmark) in 2007 and 2008. In 2007, the Paris pollen season started earlier than in Copenhagen and was slightly longer, with lower peak pollen levels. Additionally, pollen levels in the same region can differ from one season to the next, as can be seen by comparing the 2007 and 2008 counts for Paris or Prague.

Pollen counts are also subject to strong day-to-day and week-to-week variations – even during the pollen 'peak'. As can be seen in Fig. 1, the Paris 2008 season's highest daily

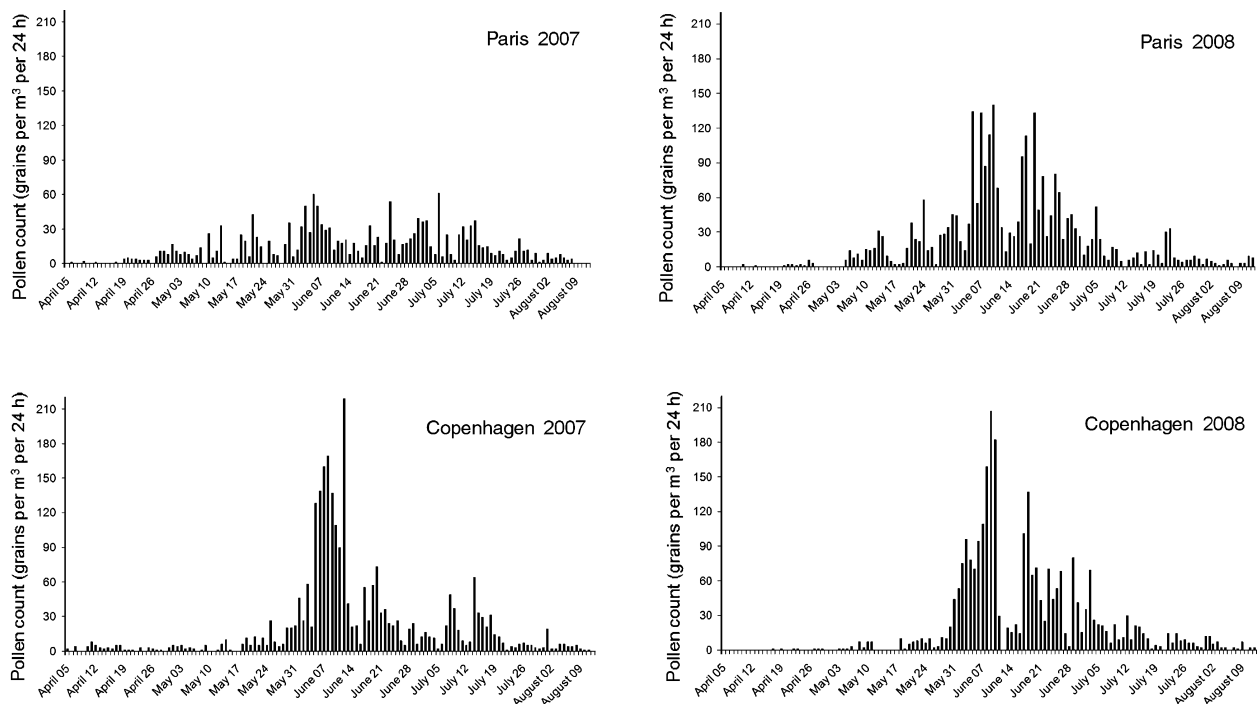


Figure 1 Variability of pollen counts from one country to another (Paris, France and Copenhagen, Denmark) and 1 year to another (2007 and 2008).

pollen counts were recorded from June 4th to 12th and from June 19th to 22nd but were separated by a few days with very low counts (related to weather conditions). Intercentre and intracentre variations in the trial subjects' exposure to allergen also result from differences in professional, school, social, leisure and sporting activities. Both the EMA and the FDA state that it is mandatory to document exposure to the relevant allergens for seasonal allergies. The FDA also states that it is also helpful to collect data on the number of rainy days and the extent of patient exposure to outdoor air (14, 15). When low pollen counts make evaluation difficult in long-term, natural-exposure studies, the EMA (14) has also suggested that controlled challenges inside an ACC can be used.

Patient inclusion and exclusion criteria

In natural-exposure trials of pollen allergen immunotherapy, treatment is typically initiated 1–6 months before the start of the season (i.e. preseasonal treatment) and then continued throughout the season (i.e. co-seasonal treatment). Patients who are essentially asymptomatic on study entry are enrolled on the basis of their stated Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) for the previous pollen season. As retrospective scoring suffers from memory bias and over-rating of the average symptom severity (17), the mean levels of symptoms in placebo groups of natural-exposure trials of pollen allergen immunotherapy are typically only low to moderate. This contrasts with the moderate-to-severe symptoms measured at the time of inclusion in symptomatic drug trials (18).

The EMA guideline (14) suggests that patients in natural-exposure clinical studies 'should experience an appropriate minimum level of symptoms and a sufficient period of persistent symptoms before enrolment. It is recommended to investigate the level of symptoms during a baseline period rather than by retrospective scoring of symptoms'. The guideline goes on to specify that 'titrated provocation tests may be useful for selecting subjects with a desired minimum level of symptoms'. The ACC approach can provide a baseline score, with accurate measurement of the symptom intensity and profile; this enables the inclusion of subjects with a high symptom score in response to allergen exposure in the ACC and who are more likely to suffer from moderate-to-severe symptoms when the pollen season starts.

Clinical studies of antihistamines, corticosteroids and leukotriene receptor antagonists in allergic rhinitis are not confronted with this difficulty, as subjects are recruited when symptomatic, during the pollen season and according to a defined severity threshold (18). The short duration of these latter clinical studies (often no more than 2 weeks) helps avoid the need for rescue medication use and reduces major variations in the pollen count.

Symptom and medication scores

The most widely used allergic rhinoconjunctivitis symptom score is the Rhinoconjunctivitis Total Symptom Score (RTSS), which typically rates each of four nasal symptoms

and two ocular symptoms. Rescue medication use is also an efficacy criterion employed in allergen immunotherapy trials, as it is proportional to the discomfort prompted by the patient's allergic symptoms. Given that natural-exposure, placebo-controlled allergy immunotherapy trials are performed over several months or even years, it is unethical to prohibit rescue medication in such cases. The rescue medication scores rate the quantity and type of medication used but differ in the number of authorized drugs, their patterns of use, the score given to each drug and whether scores are cumulative or limited to the 'strongest' drug taken on a given day. Rescue medication use reduces symptom severity and thus the symptom score. The use of a combined symptom and medication score (i.e. a combined score) is not mandatory, and so symptom and medication scores can be used as co-primary endpoints. The EMA (14) has recommended that a primary endpoint in allergen immunotherapy clinical trials must reflect both symptom severity and rescue medication use. Proposals have been made for standardizing combined scores (19, 20) and adjusting the symptom score for rescue medication use [e.g. variants of the last-observation-carried-forward method (20) and the Adjusted Symptom Score, which adjusts the RTSS to reflect rescue medication use (21)].

The allergen challenge chamber and allergen immunotherapy

The ACC is a specially designed room that enables trial participants to be exposed to a controlled environment and therefore challenges them with a defined concentration of airborne allergen (22). Use of the ACC in the allergy field was first developed in 1985 by Horak (23) at the University Clinic of Vienna (the Vienna Challenge Chamber) and has been refined since (24). Although the ACC has been extensively used to document the efficacy and onset of action of symptomatic medications [such as H1-receptor antagonists, corticosteroids and leukotriene antagonists (25–29)], this tool appears to have been underexploited in allergen immunotherapy, with very few published studies.

In 1996, Donovan et al. (30) reported on a 3-h ACC challenge with ragweed pollen for three groups of patients (16 ragweed-allergic subjects treated with ragweed SCIT for at least 2 years, 16 ragweed-allergic immunotherapy-naïve subjects and 11 nonallergic, untreated subjects). Nasal and ocular symptoms were scored every 15 min. The symptom score was higher in the allergic immunotherapy-naïve group than in the SCIT group from minute 75 ($P = 0.039$) until the end of the challenge.

In 1998, Horak et al. (31) used the Vienna Challenge Chamber to challenge birch allergy patients before and after 4 months of sublingual allergen immunotherapy or placebo. In the 2-h pretreatment challenge, there was no difference in nasal airflow between the two groups. After treatment, nasal airflow was considerably greater in the allergen immunotherapy group ($P = 0.028$).

In 2004, Horak et al. (32) again used the Vienna Challenge Chamber to evaluate the efficacy of glutaraldehyde-modified allergen extract from house dust mites adsorbed onto

aluminium hydroxide over the course of a 12-month allergen immunotherapy regimen. A marked placebo effect was evident during the first weeks of treatment. However, during the maintenance dose phase, all the challenges demonstrated a consistent difference in favour of the active immunotherapy.

Most recently, Horak et al. (13) used the ACC in a randomized, double-blind, placebo-controlled study to determine the effect and onset of action of a 300 IR 5-grass pollen sublingual allergen immunotherapy tablet. The ACC had been previously validated for grass pollen challenges of allergic rhinitis sufferers (33). Eighty-nine adults with grass pollen rhinoconjunctivitis were challenged before treatment (baseline) and after 1 week and 1, 2 and 4 months of treatment; 83 subjects completed the trial without any major protocol deviations. The study was performed during the winter, when no natural grass pollen exposure could interfere with the results. Symptoms were scored every 15 min during the challenge, and rescue medication was prohibited throughout the treatment period in general and during the challenge in particular.

A significant active vs. placebo effect was first achieved after 1 month of treatment, corresponding to the onset of action (mean $\pm$ SD RTSS: 5.9 ± 2.4 in the sublingual allergen immunotherapy group and 7.4 ± 3.0 in the placebo group; $P = 0.0042$). This efficacy was maintained through to 2 months (mean $\pm$ SD RTSS: 5.1 ± 2.9 for allergen immunotherapy and 6.2 ± 2.9 for placebo; $P = 0.02$) and then 4 months of treatment (mean $\pm$ SD RTSS: 4.8 ± 2.0 for allergen immunotherapy and 6.8 ± 2.9 for placebo; $P = 0.0007$). At the end of the 4-month study, the adjusted mean difference [95% CI] was $-1.97 [-2.99; -0.94]$. This ACC result can be put into perspective with the adjusted mean difference over the whole pollen season of $-1.4 [-2.1; -0.7]$ in a Phase III, natural-exposure studies of the same 300 IR 5-grass pollen tablet in adults (31) (mean $\pm$ SD RTSS: 3.6 ± 3.0 for allergen immunotherapy and 4.9 ± 3.2 for placebo; $P = 0.0001$). In a Phase III, natural-exposure trial of the same tablets in children (9), the adjusted mean difference [95% CI] was $-1.1 [-1.8; -0.5]$ (mean $\pm$ SD RTSS

3.2 ± 2.9 for allergen immunotherapy and 4.5 ± 2.9 for placebo; $P = 0.001$).

Optimization of the clinical development of allergen immunotherapy

The clinical development programme in allergen immunotherapy differs from conventional drug development in several respects. In Phase I studies, the tolerance of an allergen preparation is tested in allergic individuals and not in healthy volunteers. The dose-ranging investigations usually completed in Phase II in conventional drug development may, for allergen immunotherapy, extend into the pivotal Phase III studies that assess efficacy and safety in a larger number of patients. Hence, a key issue in the clinical development of allergen immunotherapy is how to optimize treatment protocols and, in particular, how to accelerate Phase II studies by rapidly determining the optimal dose and thus avoiding the need for dose ranging in natural-exposure trials.

We believe that the highly control setting of the ACC may be very valuable in the clinical development of allergen immunotherapy products by reducing the degree of dependence on natural-exposure trials (Fig. 2). The ACC enables researchers to (i) challenge patients with a defined, controlled level of allergen, (ii) characterize out-of-season symptoms or baseline symptoms immediately prior to treatment initiation, (iii) avoid the confounding effect of multiple allergens or rescue medication on symptoms and (iv) supplement subjective data (such as self-rated symptom scores) with objective measurements such as pulmonary function tests (FEV_1), nasal inspiratory flow, the amount and composition of nasal secretions, levels of immune markers in blood samples (e.g. allergen-specific immunoglobulins (IgE and/or IgG) or basophil activation), nasal lavages and allergen sensitivity skin tests (prick tests with a range of allergen concentrations for determining the threshold causing a positive skin response). Although function testing and immune marker assays can be performed in natural-exposure trials, the logistics are more complicated and patients often need to travel to

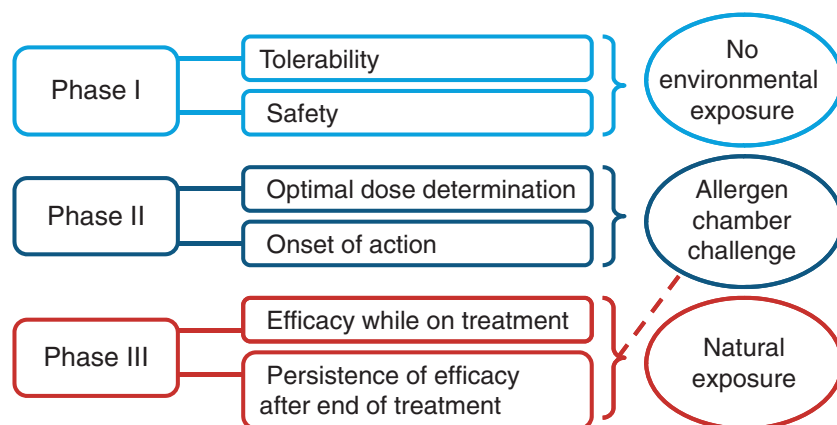


Figure 2 Use of the allergen challenge chamber in the clinical development of allergen immunotherapy.

the clinic or laboratory (with increased costs and a negative impact on work/school activities). The highly controlled conditions in an ACC again reduce variability by helping to standardize test procedures and sampling times.

The intensity of the symptom response to allergen in the ACC is expected to be greater than in natural-exposure studies (notably because of high, constant levels of allergen and the absence of rescue medication in ACC studies). The effect size is likely to be larger, with a lower variability [e.g. a coefficient of variation close to 50%, rather than the value of 70% observed in natural-exposure studies (13, 34)]. Taking into account an observed improvement of 30% (13) in the RTSS in active treatment versus placebo groups [instead of the 20% threshold recommended by the World Allergy Organization (19)] and an alpha error of 0.05 in a two-sided test, a sample of 34 patients per arm (13) had sufficient power (81%) to detect a significant difference in favour of the active treatment. This figure of 34 compares with 160 patients per arm in the natural-exposure studies (based on a coefficient of variation of 70% and a relative mean difference between active and placebo of 20%) and indicates that the ACC can provide cost and ethical benefits by reducing the sample size.

The EMA guideline (14) already states that 'provocation tests (e.g. allergen exposure in ACC) and/or clinical endpoints may be used as primary endpoints' in early-stage, dose-ranging studies (Phase II). The information gained through use of an ACC extends the available investigational period and may accelerate timelines by up to a year in clinical development programmes involving seasonal allergens.

Because of the need to test pollen allergen immunotherapies during the pollen season, natural-exposure Phase III trials often incorporate dose validation into their design (34, 35) and correspond to what would be considered as Phase IIb/III trials in most other therapeutic fields. This is a major differentiating feature of clinical development in allergen immunotherapy. Use of the ACC to validate dosing (13) means that the natural-exposure Phase III trials can focus on establishing the placebo-controlled efficacy and safety of a single active dose level. Under natural-exposure conditions,

determination of allergen immunotherapy's onset of action requires several subgroups of patients with different preseasonal protocols and the hope that the pollen season will start on the predicted date for all groups. Using an ACC, a single group of patients can be challenged repeatedly over time to identify the treatment's onset of action (13). The FDA suggests that the ACC could be used to address the onset of action for seasonal allergies (15). A further advantage of the ACC relates to the use of a single allergen in the chamber challenge; this may help identify and then take account of the effect of confounding allergens in natural-exposure trials with polysensitized patients.

Potential disadvantages of the use of an ACC in an allergen immunotherapy clinical development plan (Table 1) include the fact that few facilities are available (with two in Europe, two in Canada, one in the United States and three in Japan). Space within the ACC is also an issue, although some facilities can accommodate over 100 subjects at the same time. New bias may be introduced by these 'artificial' circumstances (claustrophobia, clues from other participants, etc.). For practical reasons, exposure times are limited to several hours. Moreover, abrupt out-of-season allergen challenges in an ACC may be considered to be a disadvantage, in view of the lack of solid information on seasonal priming effects in the scientific literature. The EMA guideline states that 'the influence of measurement within or without the pollen season (i.e. the influence of the development of inflammation related to allergen exposure duration or co-sensitization) has to be evaluated before such tests could be used as primary endpoints'.

The goal is not to replace all natural-exposure pollen allergy trials by ACC studies. Indeed, the EMA and FDA remind us that provocation tests are not validated as surrogate markers for efficacy (14, 15). Although the ACC has been technically validated for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis (33), the relationship between ACC results and natural-exposure results requires further work (notably for seasonal priming phenomena). Nevertheless, the FDA and EMA guidelines accept ACC studies in Phase II and consider

Table 1 The advantages and disadvantages of using an allergen challenge chamber in the clinical development of allergen immunotherapy

Advantages	Disadvantages
Exposure to a defined, controlled level of allergen	An invariable level of allergen is not 'natural'
Use of a single allergen in potentially polysensitized patients	Low number of operational ACCs worldwide
Out-of-season use for seasonal inhalant allergens and the ability to save up to 12 months in the development programme	Potential effects of the trial context, claustrophobia or the influence of other subjects on subjective symptom scores
Rescue medication use can be prohibited or suspended during the challenge	Short exposure times (no more than several hours)
Ability to collect biological samples from participants	A potentially abrupt challenge
Investigation into dose ranging and onset of action	Lack of seasonal priming in out-of-season challenges
Overall cost and ethical benefits because of use of lower number of subjects than in natural-exposure trials	The small numbers of subjects reduce the statistical power for some hypotheses and limit the ability to have ethnically/demographically representative populations

them of value during Phase III development. The ACC can be used to support Phase III trials in allergen immunotherapy and clarify outstanding issues (such as the onset of action and effect size) that are difficult to address in natural-exposure trials because of the number of confounders. The EMA states that provocation tests performed in parallel with clinical studies can support proof of efficacy; this is especially true in years with low allergen exposure and consequently low or no clinical efficacy but where efficacy is maintained in the ACC (14).

Conclusion

Despite recent improvements in clinical development programmes for natural-exposure trials of allergen immunotherapy, there is still room to optimize methodologies. Use of the ACC and other methodological innovations should help researchers to (i) facilitate the allergen immunotherapy dose-finding process, (ii) accelerate the transition from Phase I/II to Phase III trials using smaller number of patients, performing studies without being constrained by the pollen season and obtaining clear effects in patients with proven, high symptom scores, (iii) characterize the onset and maintenance of action, (iv) avoid the confounding effects of rescue medication and (in polysensitized patients) other allergens,

(v) better characterize the baseline or pretreatment characteristics of trial subjects, (vi) perform a wide range of better-standardized physical and laboratory measurements during an acute allergen challenge, (vii) simplify trial logistics and (viii) support (but not replace) Phase III natural-exposure trials for the investigation into long-term and disease-modifying effects. The low number of ACCs in operation (eight worldwide) could be considered as a drawback but the goal is not to test all natural-exposure trial subjects in an ACC; although additional ACCs would be of use, capacity is available in the existing facilities. The relationships between ACC data and natural-exposure data (notably in terms of symptom intensities and time scales) require further investigation. In particular, the role of seasonal priming must be clarified. The benefits of ACC use are already being applied in the clinical development of pollen (grass, birch and ragweed) and house dust mite allergen immunotherapy but are likely to be just as relevant for other inhalant allergens. These various features should increase levels of evidence for safe, easy-to-use allergen immunotherapy formulations.

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