Phase I study of subcutaneous allergen immunotherapy with *Dermatophagoides pteronyssinus* in patients with allergic rhinoconjunctivitis with or without asthma

**Aim:** A double-blind placebo-controlled study was conducted according to EMA guidelines, to evaluate safety, tolerability and short-term treatment effects of three updosing regimens of *Dermatophagoides pteronyssinus* subcutaneous allergen immunotherapy. **Patients & methods:** Forty-eight patients were randomized to groups: A (six weekly doses), B (eight weekly doses) or C (eight doses, two clustered doses over 3 weeks). **Results:** The most frequent adverse events were local reactions. No serious adverse events were found. Severe systemic reactions were reported more frequently in Group C. Decreased cutaneous responses and increased specific IgGs were shown in all active groups, even within the short-term. **Conclusion:** *Dermatophagoides pteronyssinus* subcutaneous allergen immunotherapy in depot presentation exhibited good safety and tolerability. Group A seemed to show the best profile for further clinical development.

**Keywords:** allergen • *Dermatophagoides pteronyssinus* • house dust mites • rhinoconjunctivitis • safety • subcutaneous allergen immunotherapy • tolerability

Rhinocconjunctivitis is the most common allergic condition, accounting for 55.5% of diagnoses in allergy clinics [1]. House dust mites (HDM) are complex organisms that are capable of producing thousands of different proteins and macromolecules, with a number of them being potential allergens. *Dermatophagoides pteronyssinus* (DPT) is the most prevalent HDM in Europe. According to Heinzerling et al. [2], DPT sensitization is present in about 20% of patients with rhinoconjunctivitis in Spain.

Allergen immunotherapy (AIT) is particularly recommended for patients with moderate-to-severe allergy unsuccessfully controlled by symptomatic treatment [3,4].

AIT, a type of immunomodulation, causes a reduced hypersensitivity response to certain allergens [5] and has been shown to be effective in allergic rhinitis [4] as well as in selected patients with allergic asthma [6]. AIT has been used for more than a century, but only in recent decades have double-blind controlled trials been published to prove its effects. Based on a comprehensive review, the WHO concluded that AIT was an effective and well-documented therapeutic option in allergic diseases [7]. The role of AIT was subsequently confirmed in an updated review [8].

Based on a review of more than 2700 references, an expert panel published Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines with a number of evidence-based recommendations on allergy therapy, including clinical trials showing that AIT results in clinical benefits in rhinitis and asthma [9].

Various routes of administration are available for AIT, including subcutaneous, intra-nasal and sublingual. Although all so-called subcutaneous allergen immunotherapy (SCIT) therapies share some common features, such as using allergenic extracts, a range of different products are available. They are mainly adsorbed onto aluminum hydroxide in a matrix or gel, and allergens are slowly released. Such a procedure may result in a reduced incidence and severity
of adverse effects (including local reactions, urticaria, asthma and others) [10]. The EMA guidelines do not recommend traditional Phase I trials with allergenic products in healthy volunteers, because healthy individuals do not react in the same way as allergic patients; thus, they do not reflect the target population and no useful data on safety and tolerability are obtained [11]. Furthermore, a study using different dose schedules is recommended in order to collect preliminary data on safety and tolerability, and appropriate dose-escalation schedules for AIT. In the present clinical trial, an aluminum-adsorbed DPT extract for SCIT, a highly prevalent allergen in Spain, was used, and several accelerated schedules were investigated. The main objective was to compare the tolerability and safety when administered using three different dose-escalating schedules in adult patients with allergic rhinoconjunctivitis with/without asthma sensitized to DPT. Establishing the optimal administration schedule was a secondary study objective. Surrogate efficacy markers were also assessed, in terms of immunoglobulin changes (specific IgE, IgG and IgG4) and skin tests (prick test dose response).

Patients & methods
A Phase I randomized, double-blind, placebo-controlled, trial was performed in two participating centers in Spain (Hospital Universitario La Fe, Valencia, and Hospital Basurto, Bilbao). The allergenic product used in this study was a sterile depot suspension with DPT native extract (Allergovac Depot®, Bial-Aristegui, Zamudio, Spain), which was adsorbed to 0.33% aluminum hydroxide to produce prolonged release of the allergen from the injection site. The other components were phenol, sodium chloride and water for injection. The evaluated vaccine can be considered different to previously commercialized vaccines from Bial-Aristegui, so an early clinical phase was necessary in order to obtain orientation toward dose and escalation schedule. Raw material used to obtain the *D. pteronyssinus* allergen extract was of the mite isolated bodies type instead of the previous whole mite culture type used previously. Mite bodies were isolated by sieving a harvested culture which had been grown in nonallergenic media, thus leading mainly to a different balance of the major allergens Der p 1 and Der p 2. Whole mite culture raw materials give rise to extracts with a high Der p 1:Der p 2 ratio; the preparations obtained from mite isolated bodies present a similar allergen content. Batch L-101006 was used in the current study. The maximum concentration (vial 3) of depot DPT extract was 1000 treatment standardized unit/ml (TSU/ml), equivalent to 0.5 SPT/ml and with Der p 1 and Der p 2 concentrations of 4.68 and 4.50 μg/ml, respectively. A volume of 0.5 ml of vial number 3 was injected as the maximum dose administered, resulting in doses of 2.34 and 2.25 μg of Der p 1 and Der p 2, respectively.

Selection criteria were defined according to ARIA and EMA guidelines. Patients aged 18–60 years with allergic rhinoconjunctivitis with or without asthma, sensitized to DPT at least 1 year before study onset, were selected. Main selection criteria included a DPT prick test ≥ 3 mm and a DPT-specific IgE > 0.7 kUA/L (CAP, Phadia, Uppsala, Sweden) during the past year; patients sensitized to other clinically relevant seasonal allergens having a pollination period not concurrent with the DPT SCIT administration period were eligible for the study. Patients sensitized to other clinically relevant perennial allergens showing serum IgE levels higher than 0.7 kUA/l were excluded. Patients with severe asthma or forced expiratory volume in 1 s (FEV1) less than 70%, or with asthma which required treatment with inhaled or systemic corticoids at the time of the study or in the 8 weeks immediately prior to the onset of treatment, were also excluded.

After a 4-week screening period, patients were openly randomized to three therapeutic schedules (A, B and C) in entrance order. In the same randomization, using a double-blind design, patients were allocated in each group (A, B and C) to active therapy or placebo in a 3:1 ratio (Figure 1). Doses administered ranged from 2 to 500 TSU; the content of major allergen for the maximum administered dose (500 TSU) was 2.34 μg (Der p1) and 2.25 μg (Der p2). Duration of therapy was 5, 7 and 3 weeks in A, B and C schedules, respectively. A matching placebo not containing allergen extract was used. Cumulative doses for the three arms are described in Figure 2. Patients were treated according to the schedules presented herein. Rescue drug use for symptoms was allowed over the study period:

- **Group A:** six weekly doses (over 5 weeks):
  - Vial 2: 0.1, 0.2 and 0.5 ml
  - Vial 3: 0.1, 0.2 and 0.5 ml

- **Group B:** eight weekly doses (over 7 weeks):
  - Vial 1: 0.2 ml
  - Vial 2: 0.1, 0.2 and 0.4 ml
  - Vial 3: 0.1, 0.2, 0.4 and 0.5 ml

- **Group C:** eight doses, two doses in the same day in a 30-min period (over 3 weeks):
  - Week 1: vial 2 – two 0.1 ml doses
  - Week 2: vial 2 – 0.2 and 0.3 ml
  - Week 3: vial 3 – two 0.1 ml doses
  - Week 4: vial 3 – 0.2 and 0.3 ml

Baseline demographic and clinical data were recorded, including age, weight, height, previous
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Figure 1. Patient disposition and a representation of study design. Patients per group: active 12, placebo 4.

- **Consent withdrawal**: n = 1
- **Discontinued**: n = 0
- **Adverse reaction**: n = 3
- **Concomitant disease**: n = 3
- **Completed**: n = 10
- **1 week follow-up

All reported adverse events (AEs) were recorded, regardless of their relationship with study therapy. Safety was additionally assessed with baseline and final routine laboratory analyses.

The primary end points were the number of ARs and the severity of local and systemic ARs (SARs) to SCIT administration. Proportions were compared between study arms. The tolerability of SCIT was evaluated by early and late local reactions (i.e., local swelling and redness) and systemic reactions after each injection (any symptoms from organs distant from the location of the injection). Reactions were classified depending on the severity and onset of the reaction, according to the EAACI classification [8]:

- **0**: no symptoms or nonspecific symptoms;
- **I**: mild systemic reactions, which may include symptoms like localized urticaria, rhinitis or mild asthma (PF <20% decrease from baseline);
- **II**: moderate systemic reactions, which may start greater than 15 min after the injection and may com-

personal and family history and current symptoms. Allergic rhinitis was classified as intermittent versus persistent and mild versus moderate to severe. Medication use for rhinoconjunctivitis/asthma in the last 3 months was recorded. Symptoms were assessed before and after each administration; lung function tests (spirometry) were evaluated at baseline and whenever the investigator suspected an adverse reaction (AR). Prick tests, performed using four increasing doses of DPT extracts (0.005, 0.05, 0.5 and 5 mg/ml), as well as positive (histamine) and negative (saline) controls and specific IgE and specific IgG (IgG and IgG4) to DPT, were measured before and after treatment by ELISA technique [12] at the Protein Lab of Bial-Industrial Farmacéutica S.A.

Symptoms were assessed before and 30 min after AIT was administered. Newly appearing symptoms after administration were reported as adverse reactions (ARs) in case report forms. Between visits, symptoms were recorded by patients on diary cards. Concomitant drug and rescue medication use were also recorded.
Figure 2. Cumulative doses for three different updosing regimens (groups A, B and C).
TSU: Treatment standardized unit.

prise symptoms like generalized urticaria and/or moderate asthma (PF <40% decrease from baseline);
• III: severe but not life-threatening systemic reactions, which may comprise generalized urticaria, angioedema or severe asthma (PF >40% decrease from baseline) of rapid onset (<15 min);
• IV: anaphylactic shock, which may include symptoms such as: immediate evoked reaction of itching, flushing, erythema, generalized urticarial, stridor (angioedema), immediate asthma, hypotension, etc;
• Secondary end points included immunoglobulin level determination (specific IgE, IgG and IgG4) and prick-test dose response.

Statistical analysis
Sample size estimation was based on a maximum difference between therapy arms of 50% for AEs and a 10% dropout rate. Forty-eight patients were included so that a final sample size of 43 patients could be achieved. Statistical power for AE differences in study arms was 87%, with a p-value <0.05 representing the significance level. Continuous variables were assessed with the Student’s t-test for independent samples to compare active therapy versus placebo and with the analysis of variance (ANOVA) with Bonferroni’s correction to compare therapy schedules. Categorical variables were assessed with Fisher’s exact test or the χ² test. The Student’s t-test for paired samples was used to compare baseline versus final end points within active therapy or placebo groups.

Results
Population characteristics & treatment
Table 1 presents details of patient demographic and characteristics. A total of 48 patients were randomized: 16 (12 active, 4 placebo) patients per treatment group. The mean age of patients was 31.4 years (95% CI: 28.8–34.1) with 54.2% of patients being female. The majority (81.3%) of patients were Caucasians (n = 39), 6.3% were Arabs and 12.5% Hispanics. The time since diagnosis was 5.9 years (95% CI: 3 to 8.7), and the age of onset was 25.6 years (95% CI: 22.6 to 28.5). Rhinitis was intermittent in 41.7% of patients and persistent in 58.3%. Disease was mild in 4 (8.3%) patients and moderate-to-severe in 44 (91.7%) patients. Most patients (41 [85.4%]) had used drug therapy for rhinitis and/or asthma within the last 12 months. Previous AIT had been used by 9 (18.8%) of patients, in all cases ended more than 5 years before entering in the study, as stated in the exclusion criteria. The time since diagnosis was 5.9 years (95% CI: 3 to 8.7), and the age of onset was 25.6 years (95% CI: 22.6 to 28.5). Rhinitis was intermittent in 41.7% of patients and persistent in 58.3%. Disease was mild in 4 (8.3%) patients and moderate-to-severe in 44 (91.7%) patients. Most patients (41 [85.4%]) had used drug therapy for rhinitis and/or asthma within the last 12 months. Previous AIT had been used by 9 (18.8%) of patients, in all cases ended more than 5 years before entering in the study, as stated in the exclusion criteria. A history of other forms of allergy was noted in 27 (56.3%) patients and intermittent mild asthma in 18 patients (37.5%). A family history of allergy was present in 27 (56.3%) patients. Symptoms were present in 72.9% (n = 35) of patients at the baseline visit.
No differences were found between groups for socio-demographic and clinical parameters depending on sex, therapy schedule or randomization to active treatment or placebo. Thus, groups were homogeneous at baseline.

During follow-up, only eight patients did not take any concomitant drug. Concomitant drugs included rescue medication (45.6%) and other drugs (54.4%).

Overall, 331 doses were administered (98, 126 and 107 in arms A, B and C, respectively). All patients received at least one study drug dose, and were included in the primary analysis. Thirty-six (75%) patients completed the study and received all planned doses. Two out of 36 patients completed the follow-up period despite they reached their own maximum tolerated dose, which was lower than the established dose. There was just one dropout, only one patient withdrew the consent (0.48%). This patient belonged to group A. In addition, nine patients did not complete therapy as planned due to ARs (six patients) or because of a concomitant disease (three subjects). All interruptions occurred in patients receiving active therapy. The proportion of patients receiving active therapy who completed the study as planned was significantly higher in arm A (91.6%) than in arm B (58.3%) or C (50%). Reasons for withdrawals were as follows: arm B, ARs (three patients); arm C, ARs (three patients) and other concomitant diseases (three patients). A flowchart of the study population is shown in Figure 1.

### Adverse events
At least one AE was reported by 42 (87.5%) patients during the trial, including 11/12 (91.7%) patients receiving placebo and 31/36 (86.1%) patients receiving active therapy. All patients in arm B showed at least one AE. Overall, 216 AEs were reported, which included 169 AEs in 36 patients in the active group and 47 AEs in 12 patients in the placebo group. The mean duration of reported AEs was 1.5 days (range 0–19; 95% CI: 1.1–1.9), with no difference between groups or therapies.

### Adverse reactions
Out of 216 AEs, 76 ARs (local and systemic) related to therapy were observed (23%), six of them in the placebo group. The number of ARs per group was 17.3% (17/98) in patients in group A, 23.8% (30/126) in group B and 21.5% (23/107) in group C.

The proportion of patients having ARs was significantly higher (p < 0.05) for arm B, with no differences between arms A and C. The mean number of ARs per patient was 1.6 (95% CI: 1–2.2); the median number per patient was 1.4 (range 0–13). The number of ARs was significantly higher in patients receiving active therapy (p = 0.001). No differences were found in the number of ARs per patient across study arms. The mean duration of AR was 0.6 days (95% CI: 0.34–0.9; range 0–6); no differences were observed across study arms. In relation to severity, ARs were

### Table 1. Patient demographics and characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Group A active (n = 12)</th>
<th>Group B active (n = 12)</th>
<th>Group C active (n = 12)</th>
<th>Placebo (n = 12)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>30 ± 8.5</td>
<td>29 ± 9.29</td>
<td>31 ± 8.84</td>
<td>34 ± 9.5</td>
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<td>66.67</td>
<td>33.33</td>
<td>33.33</td>
<td>50</td>
</tr>
<tr>
<td>CAP/PHADIA</td>
<td>Class 2 (%)</td>
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<td>2 (16.67%)</td>
<td>0 (0%)</td>
<td>2 (16.67%)</td>
</tr>
<tr>
<td></td>
<td>Class 3 (%)</td>
<td>6 (50%)</td>
<td>2 (16.67%)</td>
<td>3 (25%)</td>
<td>4 (33.33%)</td>
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<tr>
<td></td>
<td>Class 4 (%)</td>
<td>1 (8.33%)</td>
<td>2 (16.67%)</td>
<td>5 (41.67%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td></td>
<td>Class 5 (%)</td>
<td>2 (16.67%)</td>
<td>2 (16.67%)</td>
<td>2 (16.67%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td></td>
<td>Class 6 (%)</td>
<td>2 (16.67%)</td>
<td>2 (16.67%)</td>
<td>2 (16.67%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IgE V0 (absorbance 492 nm)</td>
<td>Mean (SD)</td>
<td>0.81 ± 0.59</td>
<td>0.77 ± 0.66</td>
<td>1.01 ± 0.86</td>
<td>0.70 ± 0.64</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>Mean (SD)</td>
<td>116 ± 13.15</td>
<td>113 ± 13.88</td>
<td>103 ± 13.05</td>
<td>115 ± 13.51</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>Mean (SD)</td>
<td>1.35 ± 2.43</td>
<td>5.41 ± 10.41</td>
<td>4.19 ± 9.47</td>
<td>11.82 ± 11.79</td>
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<tr>
<td>Previous AIT</td>
<td>% No</td>
<td>100</td>
<td>83.33</td>
<td>66.67</td>
<td>75</td>
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<tr>
<td></td>
<td>% Yes</td>
<td>0</td>
<td>16.67</td>
<td>33.33</td>
<td>25</td>
</tr>
</tbody>
</table>

AIT: Allergen immunotherapy; CAP/PHADIA: CAP IgE specific System (Phadia, Uppsala, Sweden); FEV1: Forced expiratory volume in 1 s; SD: Standard deviation.
mild in 37 cases (52.0%), moderate in 26 (37.1%) and severe in 7 (10%) with no differences across study arms. Most ARs required no action to be taken (49, 70%); 8 (11.4%) ARs required additional therapies; 6 (8.6%) required dose changes; and 7 (10%) resulted in withdrawal from the study. All ARs subsided by the end of the study.

Local & systemic ARs
There were 62 (18.7%) local ARs and 14 (4.2%) SARs among the 331 doses administered. Dose changes due to local ARs were required for two late local reactions in group A (same patient) and one late local reaction in group B, indicating that local reactions were clinically relevant in only 1% of administered doses. More than half of all patients (28 [58.3%]) had at least one local or systemic AR related to therapy, whereas 20 (41.7%) had no ARs. At least one AR was reported in 4/12 (33.3%) patients receiving placebo and in 24/36 (66.7%) receiving active therapy.

The highest proportion of patients receiving active therapy that developed local ARs was observed in arm B (p < 0.05).

A total of 14 cases of SARs were observed in ten patients (4, 6 and 4 SARs in arms A, B and C, respectively). In arm A, the severity of most SARs was grade I, as opposed to prevailing grade II or III events in arms B and C. The highest proportion of patients having SARs was observed in arm B (40%); no differences were found between arms A and C (both 30%). The mean number of SARs per patient was 1.3 (95% CI: 0.95–1.65), and the median number was 1 per patient (range 1–2). Although no significant differences were found across study arms, the mean number of SARs per patient was numerically higher in arm B.

The proportion of active doses associated with SARs was similar for the three groups (arm A: 4/98 [4.08%], arm B: 6/126 [4.76%] and arm C: 4/107 [3.74%]). The severity of SARs appeared to be lower in arm A, with three grade I and one grade II SARs (3.06, and 1% in 98 doses) compared with both arm B, with one grade I, four grade II and one grade III SARs (0.8, 3.17 and 0.8% in 126 active doses) and arm C, with one grade I, one grade II and two grade III SARs (0.93, 0.93 and 1.9% in 107 total administered doses per group).

Immunoglobulins
Specific IgG for DPT and IgG4 increased significantly in all active groups (arms A and B, p < 0.001; arm C, p = 0.001 vs placebo). Data for IgG4 and IgG levels are shown in Figures 3 & 4, respectively, after 5, 7 and 3 weeks of treatment for arms A, B and C, respectively. There were no significant differences in IgG and IgG4 increases between active groups. DPT-specific IgE was reduced (not statistically significant) in all active groups (Figure 5).

Skin prick test
Reductions in skin reactivity (wheal area) were only observed in patients receiving active treatment but not in the placebo group. Skin prick test dose response in all active therapy groups is shown in Figure 6. In group A, reduction of the wheal area was statistically significant for vial 2 (p = 0.002), vial 3 (p = 0.005) and vial 4 (p = 0.001), but not for vial 1 (p = 0.071). In group B, wheal area reductions were not statistically significant for any of the allergen concentrations tested, whereas in group C, a statistically significant reduction in wheal area was observed for vial 1 (p = 0.005).

Discussion
AIT has been used since the beginning of the 20th century. However, guidelines on the clinical development of AIT (EMA guidelines) have only been effective in recent years. According to EMA guidelines, the first step for developing a product for specific AIT is to provide data on safety and tolerability with regards to the maximum tolerated dose and suitable dose-escalation scheme. That reinforces the fact that there are not many published Phase I trials on AIT; whereas, it is more feasible to find papers on the efficacy and safety of AIT [13–15], including modification in allergic disease progression from rhinitis to asthma articles [16]. At present, there is good evidence for HDM-SCIT efficacy and its long-term effects in adults and children [17].

The present Phase I study with a depot DPT extract, which was designed as a randomized, double-blind, placebo-controlled trial and conducted according to EMA recommendations [12], provides evidence of the short-term safety and tolerability of SCIT in adult patients with allergic rhinoconjunctivitis and/or asthma.

A few Phase I studies of SCIT with HDM extracts in allergic patients have been reported. A single center, open-label Phase I/IIa study evaluated the safety, tolerability and clinical efficacy of A-type CpG oligodeoxynucleotide (QbG10) as an adjuvant to AIT with a subcutaneous HDM allergen extract in patients with HDM allergy [18]. Twelve out of 21 study subjects (57.1%) reported a total of 41 AEs, of which 59% were rated as mild, 41% as moderate and none as severe. Recently, Corzo et al. [19] investigated the tolerability and acceptable dose range of an orodispersible HDM sublingual AIT tablet for the treatment of HDM-induced asthma, with or without rhinoconjunctivitis in adults and children in two Phase I trials. Doses up to 12 development units (DU) were tolerated in the
selected populations, and thus considered suitable for further clinical investigation. No serious AEs were reported. In trial 1 (maximum dose, 32 development units [DU]), 1 patient in the 16 DU group discontinued, and the entire 32 DU group was discontinued as one patient had a severe adverse reaction. In trial 2, no serious AEs were reported.
2 (maximum dose, 12 DU), no patients discontinued prematurely. Mild AEs related to the administration site (oral pruritus, stomatitis, oral paresthesia, mouth edema, throat irritation) were the most frequent. Data from these studies [18,19], regarding the occurrence of ARs, are difficult to be compared with the present findings because of differences in the extracts tested, QbG10 as adjunct to HDM in one study [18] and the use of an orodispersible HDM sublingual tablet in the other [19].

The aim of the current study was to find the most suitable updosing scheme in terms of safety and tolerability. Different dose schedules were tested in our study with the same maximum dose (500 TSU) but different cumulative doses in each group. Besides this, exploratory trial was designed to provide a trend to select the most adequate dose-escalation scheme to continue with the clinical development of our vaccine, thus, no statistically significant between-group differences results were anticipated. The overall rate

Figure 5. Specific immunoglobulin IgE level changes in all groups: active and placebo.

Figure 6. Changes in skin prick test response: changes in wheal area (mm²) per group of treatment (groups A, B and C) between final visit and basal visit versus its placebo.

Change in wheal area (mm²)
The incidence of SARs found in our study was similar to data reported previously in a Cochrane review of SCIT for seasonal allergic rhinitis [4]. Thus, based on data of systemic ARs, treatment schedule of group A seems to be associated with the most favorable profile in terms of safety and tolerability.

Apparent, the more doses that are administered, the higher the expected risk of ARs; however, this is not the only factor that interferes with the number of ARs. In addition to the type of build-up schedule, the dose increasing steps may also influence the number of ARs. In fact, although the number of administered doses of conventional and cluster therapy was the same, the number of adverse reactions was 6 and 4, respectively. This confirmed that there are many factors, apart from the number of administered doses, which affect the number of ARs.

In all study arms, after treatment with DPT extract, allergen-specific IgG and IgG4 levels increased significantly only in the active therapy groups but not in the placebo group. However, changes in specific IgE levels were not significant in all three study regimens. It is worth to mention that IgG4 basal levels for patients in placebo allocated to group A were significantly higher than other groups. It could have been because one of the patient received AIT for 3 years, 5 years before entering in the study.

Studies with allergen SIT generally provide immunologic data at 1 year of treatment [13,15] but, in this study, immunologic changes were assessed over a short time period, which represents a novel aspect of the current study. Furthermore, as occurs with the immunoglobulin changes, most of the published studies provide data on skin reactivity to 1 year [13]. Present study results showed that in active groups A and B, skin sensitivity was reduced, with the arm A dose escalation scheme showing significant differences.

**Conclusion**

Based on our results, SCIT with a DPT extract in a depot preparation has shown a good safety and tolerability profile for all tested dosing schedules. However, the arm A schedule appears preferable based on the following findings: safety results showed that grade II–III SARs only occurred in arms B and C; the number of withdrawals was lower in arm A; prick test dose-response results demonstrated a significant wheal area reduction with all but one of the tested doses. Immune efficacy was achieved by all three schedules, with statistically significant increases in IgG and IgG4 compared with placebo.

**Future perspective**

Although AIT for allergic disease has developed over more than a century, only recently have solid evidence-based data been available, with the achievement of substantial improvements in the quality of clinical studies. In the near future, it is anticipated that existing internationally agreed guidelines for AIT and evidence-based recommendations will be used more extensively and will undoubtedly improve therapeutic outcomes in specific clinical scenarios.

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**Executive summary**

- This randomized, double-blind, placebo-controlled study, conducted according to EMA guidelines, provides preliminary data on the safety and tolerability of different dose-escalation schedules of subcutaneous allergen immunotherapy (SCIT) with *Dermatophagoides pteronyssinus* (DPT).
- A total of 48 patients (16 [12 active/four placebo] per treatment group) received 331 doses of SCIT DPT.
- Overall, 76 (23%) adverse reactions were reported (six with placebo administration), most of which were local (18.7%), and 1% were clinically relevant, and only 14 systemic adverse reactions (4.2%) were observed in ten patients receiving active therapy.
- After treatment with DPT extract, allergen-specific immunoglobulin IgG and IgG4 levels increased significantly in patients receiving active therapy in all groups.
- Reductions in wheal area were only observed in patients receiving active treatment but not in the placebo group and achieved statistical significance in group A.
- Short-term effects of SCIT with DPT extract in a depot form demonstrated a good safety and tolerability profile, and induced significant changes in both humoral and skin-prick dose response. Group A showed less severe adverse reactions compared with groups B and C.
- Among the tested schedules, arm A showed the best tolerability and efficacy profile compared with arms B and C.
At the same time, clinical trial designs based on regulatory agency recommendations will help to define the best dose, formulation, composition, release form and route of administration for SCIT products. SCIT products have become a very promising therapeutic tool in the management of allergic diseases and it is anticipated that their acceptance and use will continue to increase in the coming years.

Financial & competing interests disclosure
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References
Papers of special note have been highlighted as:

• of interest


• Study selection criteria were based on these EAACI subcommittee practical guidelines.


• These ARIA guidelines were key for the diagnosis of rhinoconjunctivitis.


• EMA guidelines that were critical for the design of our study and for establishing end points and study duration.


18 Senti G, Johansen P, Haug S et al. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific


- Despite the fact that this study evaluated allergen immunotherapy using sublingual tablets, rather than subcutaneous allergen immunotherapy, this is an important study because it is one of the few published Phase I studies evaluating allergen immunotherapy for allergic disease.
