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# Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results

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**Background:** European studies provide a preponderance of evidence for sublingual allergen immunotherapy (SLIT) safety and efficacy, but they use allergen products that differ from those expected to be approved in the United States.

**Objective:** To determine the safety and tolerability of 4 US-licensed standardized SLIT allergenic extracts.

**Methods:** Adults 18 to 50 years old with allergic rhinitis with or without asthma due to timothy grass pollen, short ragweed pollen, house dust mite, or cat hair allergy completed a single-session dose escalation followed by an 8-week, open-label daily course of SLIT. Participants documented the presence and severity of adverse effects and adherence using a daily electronic diary.

**Results:** Ninety-one participants initiated treatment, and 77 completed the phase 1 testing. Maximum tolerable doses ranged from 50 to 2,090 BAU for cat hair and dust mite extract, 31 to 91 Amb a 1 Units for short ragweed pollen extract, and 50 to 21,090 BAU for timothy grass pollen extract. During the 8-week treatment course, 98.9% of participants reported at least 1 mild, 70.4% at least 1 moderate, and 13.6% at least 1 severe adverse effect. Most adverse effects (94.6%) were rated as mild, 5.2% as moderate, and 0.1% as severe; nasal and oral-mucosal adverse effects were most commonly reported. No life-threatening adverse reactions occurred in more than 4,500 administered doses.

**Conclusions:** Daily sublingual-oral dosing of standardized allergenic extracts at maximum tolerable doses was generally well tolerated. These results are a first step toward establishing the safety of US-licensed SLIT extracts when appropriately self-administered and monitored.

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## INTRODUCTION

Allergic rhinitis (AR), an inflammation of the nasal membranes characterized by symptoms of sneezing, itching, nasal congestion, and rhinorrhea, affects 10% to 30% of adults and up to 40% of children in the United States.<sup>1</sup> It is associated with substantial morbidity, including sleep disturbances, daytime somnolence, absenteeism and decreased productivity, and increased risk of chronic sinusitis, asthma, and otitis media with effusion.<sup>2</sup>

Research indicates that an appropriate course of subcutaneous allergen-specific immunotherapy (SCIT) effectively relieves allergy symptoms,<sup>3</sup> provides long-lasting benefit,<sup>4–11</sup> and prevents the development of new allergies<sup>8,9,12</sup> and asthma.<sup>13–16</sup> Despite these benefits, concerns about serious systemic adverse reactions and the inconvenience of the treat-

ment regimen have limited the widespread adoption of SCIT.<sup>17</sup>

To address these limitations, researchers have developed alternative routes of allergen immunotherapy delivery, including the sublingual-oral self-administration of allergenic extracts (SLIT),<sup>18,19</sup> whereby sublingual drops or soluble tablets containing allergen are held under the tongue for 1 to 2 minutes, allowing absorption through the sublingual mucosa; the remainder is then usually swallowed. Evidence supports the effectiveness of SLIT in patients with AR and, to a lesser degree, those with allergic asthma.<sup>1,19,20</sup> Although SLIT delivers allergens at doses up to 500 times the cumulative monthly doses administered by SCIT,<sup>19</sup> the rate of systemic adverse reactions is 1/10 to 1/100 of that reported for SCIT.<sup>21</sup> The popularity of SLIT is increasing across Europe,<sup>22</sup> and evidence for its safety and efficacy is predominantly based on studies using European allergens. In support of future US availability of standardized sublingual allergenic extracts, a phase 1 dosing and safety study was conducted.

## METHODS

### Study Design

The design of the phase 1 testing is shown in Figure 1. The design was an open-label, dose-escalation study of 4 currently licensed (Greer Laboratories) standardized allergenic extracts—timothy grass pollen (*Phleum pratense*), cat hair (*Felis domesticus*), house dust mite (*Dermatophagoides farinae*), and short ragweed pollen (*Ambrosia artemisiifolia*)—in

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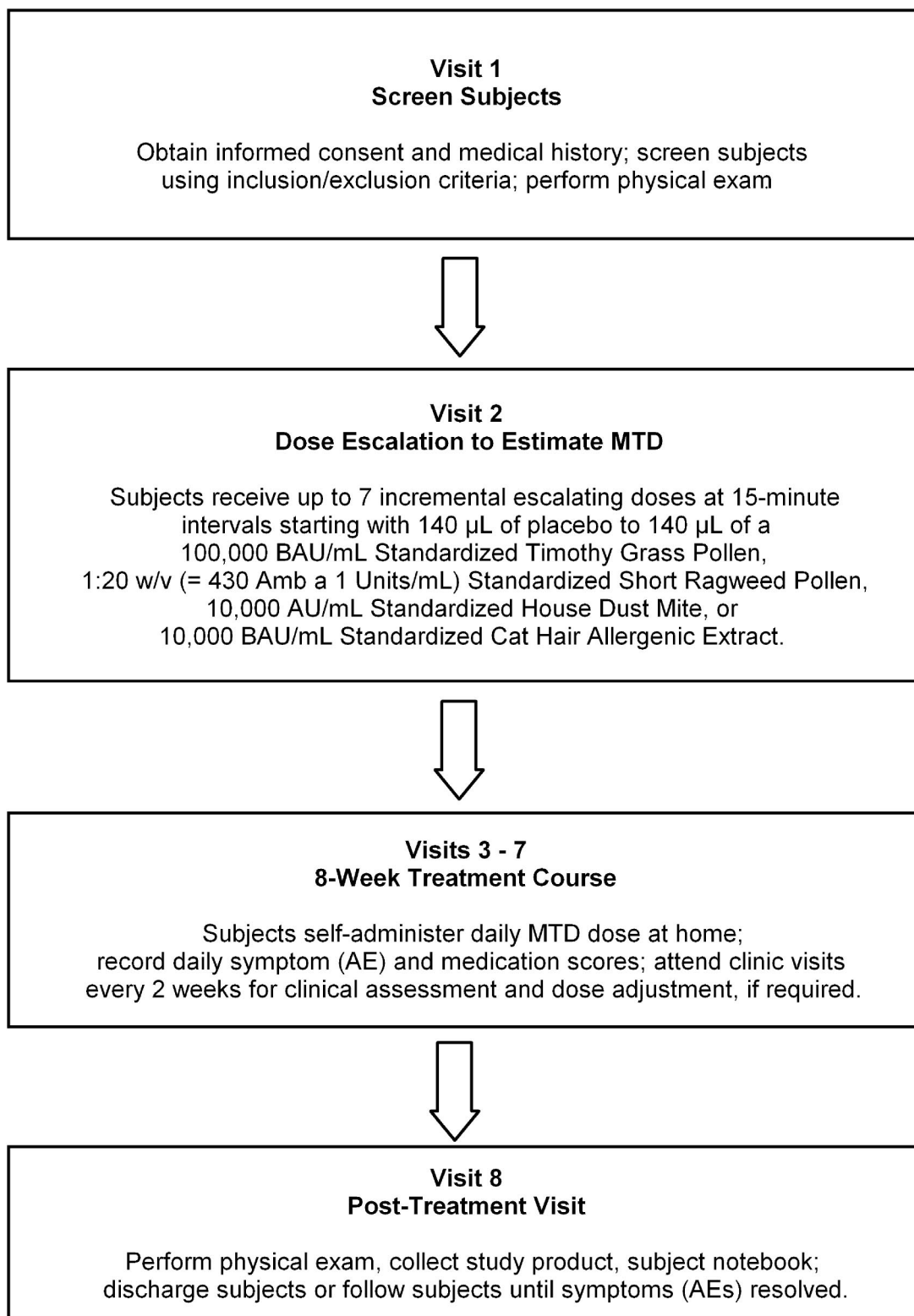


Figure 1. Flowchart for the safety evaluation of licensed Greer Laboratories standardized allergenic extracts administered via the sublingual-oral route. AE indicates adverse event; MTD, maximum tolerable dose.

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individuals diagnosed as having AR with or without asthma. Each lot of extract was tested and released according to Food and Drug Administration (FDA)-approved potency assays. The final container-closure system was equipped with a metered-dose pump and a sublingual actuator to ensure accurate dosing.

Eligible participants were aged 18 to 50 years, had a history of seasonal or perennial AR with or without asthma for at least 1 year before participating, and demonstrated sensitivity to the relevant allergen documented by a positive skin prick test result (mean wheal diameter 2 mm greater or a mean erythema diameter 2 mm greater than that elicited by the negative control [saline] at 15–20 minutes). Participants with a history of asthma must have been free of symptoms for at least 2 weeks, with forced expiratory volume in 1 second and peak expiratory flow greater than or equal to 80% of predicted at study initiation.

Exclusion criteria included use of a rescue medication (eg, albuterol) more than twice a month; history of anaphylaxis; current unstable angina, significant arrhythmia, uncontrolled hypertension, chronic sinusitis, or other chronic or immunologic diseases possibly interfering with evaluation of the test drug or posing additional risk to the patient; experimental drug use within 30 days of study entry or during the study; current use of tricyclic antidepressants or  $\beta$ -blockers; long-term use of corticosteroids; current use of medications that could induce adverse gastrointestinal reactions; pregnancy or breastfeeding; and a plan to leave the study area for more than 7 consecutive days.

Most prescription antihistamines and any nonprescription medications containing chlorpheniramine, clemastine, or diphenhydramine were withheld for at least 72 hours before study initiation. Nonprescription cough suppressants, ophthalmologic products, anti-inflammatory agents, nonsteroidal anti-inflammatory agents, and antihistamines and decongestants were not permitted unless required to treat moderate-to-severe adverse effects.

The study was conducted between February 1 and December 7, 2005. Participants with seasonal allergies were scheduled to receive SLIT outside the peak allergen season, depending on their geographic location, to ensure that symptoms experienced during the study were not attributable to environmental allergen exposure. Patients with timothy grass allergy received treatment during February to April, ragweed allergy during March to July, house dust mite during February to July, and cat hair during March to December.

#### *Preliminary Dosing Visit*

Participants received up to 7 incremental escalating doses administered 15 minutes apart, starting with 140  $\mu$ L of placebo and ending with 140  $\mu$ L of the highest available concentration of licensed standardized allergenic extract. Of US standardized extracts, only cat and ragweed are standardized by major allergen. The potency of dust mite and pollen extracts is standardized using allergy units (AU) and bioequivalent allergy units (BAU), respectively. The highest

concentration for each allergenic extract was 100,000 BAU/mL for timothy grass pollen, 10,000 BAU/mL with 15 Fel d 1 U/mL for cat hair, 10,000 AU/mL for house dust mite, and 1:20 wt/vol with 430 Amb a 1 U/mL for short ragweed pollen extract.

Adverse effects were reported by means of electronic diary after each dose. Dose escalation continued according to schedule until the maximum tolerable dose (MTD), defined as the dose eliciting moderate adverse effects or the maximum study dose, was reached. Participants returned the following day to report additional delayed adverse effects.

#### *8-Week Treatment Course*

Participants received a vial of standardized allergenic extract, 2 EpiPens (Dey LP, Napa, California), 1 electronic diary (LogPad; PHT Corp, Charlestown, Massachusetts), a notebook (for recording use of rescue medications), and written instructions regarding the proper use, storage, and administration of the extract. Participants were instructed to complete the electronic diary before and approximately 12 hours after administering the morning SLIT dose equal to the MTD and to immediately report any severe adverse effects.

Participants returned for biweekly office visits. During these visits, before which participants refrained from taking their morning dose, the investigator reviewed the patient diaries, performed an oral examination, and determined the need for dose adjustments conducted in 3-fold dose increments or decrements. The dose was reduced if a severe adverse effect occurred or if moderate adverse effects occurred on 3 consecutive days. The dose was increased if no adverse effects occurred or if mild or moderate adverse effects occurred on fewer than 3 consecutive days.

#### *Study Termination*

Treatment was terminated for any participant who had a serious adverse event, withdrew consent for any reason, refused to comply with the protocol, or reported “moderate” adverse effects with the lowest study dose (placebo). On study completion or early withdrawal, all the participants underwent a physical and oral examination and were discharged if reporting only mild or no adverse effects at the last office visit. Those reporting moderate or severe adverse effects at study termination required biweekly follow-up until resolution, after which they were discharged from the study.

#### *Evaluation of Adverse Effects*

The definition of “adverse effect” paralleled the FDA definition of adverse event (any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product and that may or may not have a causal relationship with the treatment).<sup>23</sup> In the morning and evening, participants completed a daily electronic diary checklist that rated adverse effect presence and severity, including eye (itching, swelling, tearing), nasal (itching nose, sneezing, running nose, stuffy nose), mouth/throat (itching mouth, irritated throat, cough due to mouth/throat itching/irritation), lung (lung cough, wheezing, shortness of breath,

chest discomfort), and gastrointestinal (nausea, vomiting, cramps, diarrhea) effects and ear pruritus and rash. Adverse effects were rated on a scale from 0 to 3 (0 = no evident adverse effects, 1 = mild [clearly present, minimal awareness, and easily tolerated], 2 = moderate [definite awareness, bothersome but tolerable, requiring antihistamine therapy], and 3 = severe [hard to tolerate, caused interference with activities of daily living or sleep, prompted a call to the study physician]). Participants also were asked to describe and rate the severity of any other adverse effects experienced, and investigators rated the presence or absence of signs and symptoms of allergic reactions during study visits.

#### Adherence and Data Analysis

Adherence was self-reported by electronic daily diary and was calculated as the number of days in which treatment was administered divided by the total number of treatment days. Patient-reported adverse effects were analyzed descriptively. Approximately 50 morning and 50 afternoon adverse effect checklists were expected from each participant for 56 total treatment days.

## RESULTS

### Participant Characteristics

Participants included 9 individuals allergic to timothy grass, 25 to house dust mite, 25 to short ragweed, and 32 to cat hair (Table 1). Although we used a fairly liberal criterion to define a positive skin test reaction, all but 2 participants met the more commonly applied criterion of a wheal 3 mm greater in diameter than the control, and all but 3 participants had a wheal at least 4 mm greater in diameter than the control. The 2 participants with a skin wheal less than 3 mm greater than the control had erythema diameters 7 and 20 mm greater than the control. All but 3 participants, who were withdrawn after reporting moderate adverse effects at the lowest study dose (placebo) during the preliminary dosing visit, initiated the 8-week treatment. Four participants had experienced previous allergen immunotherapy; of these, 3 completed SCIT more than 15 years ago and 1 completed SCIT approximately 1 year before participating in this SLIT phase 1 study.

### Withdrawals During 8-Week SLIT Treatment

Eleven participants (4 treated with ragweed, 5 with cat hair, and 2 with timothy grass) who initiated 8-week treatment did not complete the study. Two participants treated with ragweed and 2 with cat hair were withdrawn owing to noncompliance, and 7 participants (2 treated with ragweed, 3 with cat hair, and 2 with timothy grass) were withdrawn owing to adverse effects. Of these 7 withdrawals, 2 were judged not to be related to SLIT. The adverse effects thought to be possibly or probably related to SLIT included a severe stuffy nose and shortness of breath after the first dose; moderate chest congestion possibly due to a cold; a moderate rash; worsening of acne; and allergy to cat hair and severe nasal, oral, and chest adverse effects at the lowest allergen dose (this person later admitted to having kept a cat at home during the study).

### Dose Escalation and Determination of MTD

The highest study dose was reached during the preliminary dosing visit by 33% of participants treated with timothy grass pollen extract, 40% with ragweed pollen extract, 80% with house dust mite extract, and 69% with cat hair extract (Table 2). During dose escalation, 55% of the participants reported only mild or no adverse effects and 45% reported 1 or more moderate adverse effects; no severe ratings were reported by any participant.

### Adherence

The overall mean adherence for reporting morning and evening adverse effects using the electronic diary was 81% for timothy grass, 86% for ragweed, 88% for house dust mite, and 82% for cat hair allergy participants during 8-week treatment.

### Adverse Effects Evaluated During 8-Week Treatment

Across 8 weeks, a total of 7,636 daily checklists were completed by 88 participants, yielding 24,756 adverse effects rated as mild, moderate, or severe. All the participants reported at least 1 adverse effect on the daily checklist, with 98.9% reporting at least 1 mild, 70.4% at least 1 moderate, and 13.6% at least 1 severe adverse effect. Of the 24,756

Table 1. Participant Characteristics

Characteristic	Timothy grass (n = 9)	Short ragweed (n = 25)	House dust mite (n = 25)	Cat hair (n = 32)	All participants (N = 91)
Sex, No. (%)					
M	3 (33)	14 (56)	8 (32)	8 (25)	33 (36)
F	6 (67)	11 (44)	17 (68)	24 (75)	58 (64)
Rhinitis and asthma diagnosis, No. (%)	3 (33)	8 (32)	8 (32)	9 (28)	28 (31)
Age, mean, y	24.4	30.1	36.6	33.8	32.3
Race, No. (%)					
White	7 (78)	25 (100)	24 (96)	28 (88)	84 (92)
Black	2 (12)	0	1 (4)	1 (3)	4 (4)
Hispanic	0	0	0	3 (9)	3 (3)
Allergen specific IgE, mean (SD), kU/L <sup>a</sup>	8.74 (10.93)	4.96 (5.13)	5.28 (8.35)	19.56 (51.01)	8.68 (24.64)

<sup>a</sup> Allergen specific IgE assays were conducted by Greer Laboratories using ImmunoCAP100 (Phadia, Portage, Michigan).

Table 2. Maximum Tolerable Dose Achieved During Single-Session Dose Escalation

	Dose level <sup>a</sup>						
	1	2	3	4	5	6	7
<b>Timothy Grass–Allergic Participants (n = 9)</b>							
Concentration, BAU/mL	0	1,000	1,000	10,000	10,000	100,000	100,000
Volume, $\mu$ L	140	50	140	50	140	50	140
Dose, BAU	0	50	140	500	1,400	5,000	14,000
Cumulative dose, BAU	0	50	190	690	2,090	7,090	21,090
Participants, No. (%)	0	1 (11)	2 (22)	2 (22)	1 (11)	0	3 (33)
<b>Short Ragweed–Allergic Participants (n = 25)</b>							
Concentration, U/mL	0	4.3	4.3	43	43	430	430
Volume, $\mu$ L	140	50	140	50	140	50	140
Dose, U	0	0.22	0.60	2.10	6.02	21.50	60.20
Cumulative dose, U	0	0.22	0.82	2.97	8.99	30.49	90.69
Participants, No. (%)	0	0	0	3 (12)	4 (16)	8 (32)	10 (40)
<b>House Dust Mite–Allergic Participants (n = 25)</b>							
Concentration, AU/mL	0	1,000	1,000	10,000	10,000		
Volume, $\mu$ L	140	50	140	50	140		
Dose, AU	0	50	140	500	1,400		
Cumulative dose, AU	0	50	190	690	2,090		
Participants, No. (%)	0	1 (4)	1 (4)	3 (12)	20 (80)		
<b>Cat–Allergic Participants (n = 32)</b>							
Concentration, BAU/mL	0	1,000	1,000	10,000	10,000		
Volume, $\mu$ L	140	50	140	50	140		
Dose, BAU	0	50	140	500	1,400		
Cumulative dose, BAU	0	50	190	690	2,090		
Participants, No. (%)	0	2 (6)	3 (9)	5 (16)	22 (69)		

<sup>a</sup> Sublingual allergen immunotherapy dose levels 2 to 7 are equivalent to 10 to 100 times the subcutaneous allergen-specific immunotherapy monthly cumulative dose.

adverse effects reported, 94.6% were rated as mild, 5.2% as moderate, and 0.1% as severe.

An additional 20 adverse effects not listed on the daily adverse effect checklist were reported by 12 participants and were judged by the clinical investigator as attributable to SLIT; of these 20 adverse effects, 8 were rated as having no effect, 11 as mild, and 1 as moderate. Of the 12 adverse effects with a mild or moderate severity rating, 4 were categorized as mouth/throat effects, 3 as skin effects, and 1 as a gut effect, and 4 adverse effects constituted a new category (headache).

Table 3 gives the frequency of different types of adverse

Table 3. Types of Adverse Effects Reported During 8-Week Treatment

Category	No. (%)
Nose	12,515 (50.5)
Mouth and throat	4,478 (18.1)
Eye	4,099 (16.5)
Lung	2,066 (8.3)
Ear	1,052 (4.2)
Gut	420 (1.7)
Skin	142 (0.6)
Headache	4 (0.02)

effects and includes those reported on the daily checklist (n = 24,756) and those not reported on the checklist (n = 20). Local adverse effects (those affecting the eyes, nose, mouth/throat, gut, or ear) were the most common, accounting for 90.9% of all adverse effects; systemic adverse effects (those affecting the lungs or skin) accounted for 9.1% of all adverse effects. The prevalence, type, and severity of adverse effects were similar for patients diagnosed as having AR alone and those with coexisting AR and asthma.

During 8-week treatment, 12 participants (1 treated with house dust mite, 2 with ragweed, 3 with timothy grass, and 6 with cat hair extract) reported a total of 34 severe adverse effects. In addition, 3 participants were withdrawn from the study due to severe adverse effects; all other severe adverse effects resolved spontaneously or with dose adjustment or temporary discontinuation. Emergency intervention was required for a participant with cat hair allergy who reported severe sneezing, itchy nose, runny nose, stuffy nose, itchy mouth, ear pruritus, shortness of breath, and chest discomfort on day 8 of the treatment course at dose level 2 (50 BAU), approximately 8 hours after dosing. The patient was treated at an emergency department for suspected anaphylaxis, was observed for approximately 3 hours, and was discharged with instructions to discontinue SLIT. The patient denied taking

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any new medications or eating any new foods before this event but acknowledged owning a cat during the study.

#### *SLIT Dose Adjustments*

Dose adjustments were made in 31 of 88 participants (35%). Twenty participants had their dose increased without ill effects, except 1 patient who required a subsequent reduction in the original dose level. Twelve patients experienced dose decreases, and one-third of this group increased the dose back to the original level.

## **DISCUSSION**

These phase 1 results indicate that daily sublingual-oral administration of 4 different US-licensed standardized allergenic extracts at MTDs and up to more than 100 times the cumulative monthly doses currently used in SCIT is generally safe and without serious adverse effects. Consistent with the results of other SLIT studies,<sup>19,20</sup> most adverse effects reported in the present study were local, mild to moderate in severity, and self-resolving. Of the more than 4,500 doses of SLIT administered in 91 participants, severe adverse effects were reported in 12 participants at a rate of 7.5 per 1,000 doses, and no life-threatening adverse reactions or those requiring epinephrine occurred. The frequency and types of adverse effects were similar across the different extracts, but a greater proportion of patients receiving dust mite and cat extracts compared with pollen extracts achieved the MTD, possibly owing to the lower biological potency of dust mite and cat vs pollen extracts.<sup>17</sup> In addition, the prevalence, type, and severity of adverse effects were similar in patients with AR only compared with those with AR and asthma. Finally, similar to previous studies,<sup>24,25</sup> adherence to this self-administered in-home therapy was very good, with more than 80% of the doses taken.

Rates of adverse effects reported in SLIT clinical trials vary widely.<sup>19,26,27</sup> Such variation may be due to treatment-related factors (such as modes of administration, biological potencies, dosing schedules, use of premedication, and patient selection criteria)<sup>19</sup> or to definitions and methods of measuring adverse effects.<sup>28,29</sup> Previous SLIT clinical trials<sup>30–34</sup> that reported either an absence or a small number of adverse effects often did not define the term or provide methods of evaluation. In contrast, several other clinical trials, which defined adverse effects similarly to the FDA and this study, reported the occurrence of adverse effects (mainly oral pruritus, mouth edema, nasopharyngitis, ear pruritus, and throat irritation) in 80% to 90% of patients taking a sublingual grass allergen tablet; most adverse effects were mild or moderate.<sup>26,27</sup> A daily diary symptom checklist was used in this study to evaluate the frequency of adverse effects, a method shown to yield the highest rate of adverse effects.<sup>28,29</sup> The frequent occurrence of mild local reactions to SLIT (eg, mouth and throat itching and irritation) seen in the present study and in others using similar methods is likely a predictable consequence of exposing allergic persons to substances to which they have specific allergies.<sup>35</sup>

Although mild-to-moderate adverse effects in response to SLIT may be common and predictable, serious, life-threatening adverse reactions to SLIT are rare.<sup>19</sup> Herein, there were no life-threatening reactions to SLIT, although in 1 patient emergency intervention was needed. Although this event was judged to be possibly related to SLIT, the patient was receiving a very low dose of SLIT and later acknowledged having a cat in her home during the trial, which may have contributed to the onset and severity of this event. In the only published study of anaphylaxis after SLIT in the United States, anaphylaxis occurred in a patient with multiple allergies who received a mixture of 4 nonstandardized and 2 standardized extracts.<sup>36</sup> The patient experienced generalized pruritus, swelling of her hands and feet, and dyspnea. She self-administered an antihistamine and nebulized albuterol, and a course of prednisone controlled her symptoms.

This study has several limitations. First, this phase 1 study lacked a control group, making it impossible to determine the potential contribution of a placebo effect on the observed rates of adverse effects. Previous controlled studies<sup>26,27</sup> of SLIT have found adverse effects reported by 64% to 86% of patients in the placebo group, which did not significantly differ from the rates reported by patients receiving SLIT. Second, the methods used to evaluate and count adverse effects likely resulted in a liberal estimate of risk. For example, each adverse effect evaluated using a daily diary checklist and occurring over multiple consecutive days was counted as a separate event in this study. Third, although it was assumed that those participants' symptoms were due to an allergic response rather than to an innate immune response, this premise remains uncertain. The only means of testing this assumption would be to conduct a similar study in a double-blind manner and include a group of nonallergic controls. Finally, owing to the relatively small and racially/ethnically homogeneous sample, caution must be exercised in generalizing results to the broader population.

In conclusion, the results of this phase 1 study constitute the first step toward establishing the safe home-based self-administration of US-standardized oral-sublingual allergenic extracts provided that patients are routinely monitored by experienced physicians. Additional controlled clinical trials are under way to demonstrate the efficacy and safety of this therapy in a larger and more diverse group of patients.

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