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.

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. 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.

Research indicates that an appropriate course of subcutaneous allergen-specific immunotherapy (SCIT) effectively relieves allergy symptoms, provides long-lasting benefit, and prevents the development of new allergies and asthma. Despite these benefits, concerns about serious systemic adverse reactions and the inconvenience of the treatment regimen have limited the widespread adoption of SCIT.

To address these limitations, researchers have developed alternative routes of allergen immunotherapy delivery, including the sublingual-oral self-administration of allergenic extracts (SLIT), 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. Although SLIT delivers allergens at doses up to 500 times the cumulative monthly doses administered by SCIT, the rate of systemic adverse reactions is 1/10 to 1/100 of that reported for SCIT. The popularity of SLIT is increasing across Europe, 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
Visit 1
Screen Subjects
Obtain informed consent and medical history; screen subjects using inclusion/exclusion criteria; perform physical exam

Visit 2
Dose Escalation to Estimate MTD
Subjects receive up to 7 incremental escalating doses at 15-minute intervals starting with 140 μL of placebo to 140 μL of a 100,000 BAU/mL Standardized Timothy Grass Pollen, 1:20 w/v (= 430 Amb a 1 Units/mL) Standardized Short Ragweed Pollen, 10,000 AU/mL Standardized House Dust Mite, or 10,000 BAU/mL Standardized Cat Hair Allergenic Extract.

Visits 3 - 7
8-Week Treatment Course
Subjects self-administer daily MTD dose at home; record daily symptom (AE) and medication scores; attend clinic visits every 2 weeks for clinical assessment and dose adjustment, if required.

Visit 8
Post-Treatment Visit
Perform physical exam, collect study product, subject notebook; discharge subjects or follow subjects until symptoms (AEs) resolved.

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.
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, 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 β-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 μL of placebo and ending with 140 μL 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). 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

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*Allergen specific IgE assays were conducted by Greer Laboratories using ImmunoCAP100 (Phadia, Portage, Michigan).
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 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...
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 ef-
facts, 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 ad-
ministration of 4 different US-licensed standardized allergen-
ic 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,19,20 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 extracts compared with pollen extracts achieved the MTD, a greater proportion of patients receiving dust mite and cat adverse effects were similar across the different extracts, but requiring epinephrine occurred. The frequency and types of adverse effects likely resulted in a liberal estimate of risk. For example, each adverse effect evaluated using a daily diary check-
list 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 re-
sponse, 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-ad-
ministration 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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REFERENCES


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