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## Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults

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### ABSTRACT

**Background:** Ragweed is an important cause of allergic rhinitis with or without conjunctivitis (AR/C) in North America and elsewhere. Allergen immunotherapy enabling safe patient self-administration is considered an unmet clinical need. Allergy immunotherapy tablet (AIT) treatment has shown promising efficacy and safety for grass allergy but has not been assessed for ragweed allergy.

**Objective:** To evaluate efficacy and safety of 2 short ragweed AIT doses in patients with AR/C.

**Methods:** Adults with ragweed pollen-induced AR/C were randomized 1:1:1 to daily ragweed AIT (6 or 12 Amb a 1 units) or placebo before, throughout, and after ragweed season (approximately 52 weeks). Patients could use predefined allergy rescue medications in season. Efficacy end points included peak and entire season total combined score (TCS) and its components daily symptom score (DSS), and daily medication score (DMS). Safety assessments included adverse events.

**Results:** A total of 565 patients were randomized. During peak season, the 6- and 12-Amb a 1 unit ragweed AIT doses showed 21% (–1.76 score) and 27% (–2.24 score) improvement in TCS vs placebo ( $P < .05$ ). The 6- and 12-Amb a 1 unit AIT doses significantly improved DSS and DMS vs placebo ( $P < .05$ ). Peak and entire season efficacy were comparable. The 12-Amb a 1 unit AIT dose reduced peak-season TCS vs placebo by 21% and 25% in subgroups with and without local application-site reactions, respectively. Most treatment-related adverse events were mild, oral reactions; no systemic allergic reactions were reported. One patient in the 6-Amb a 1 unit group received epinephrine at an emergency facility for sensation of localized pharyngeal edema.

**Conclusion:** In this trial, ragweed AIT was effective and well tolerated in ragweed-allergic North American adults.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00783198.

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### Introduction

The pollen of short ragweed (*Ambrosia artemisiifolia*; common ragweed) is one of the most prevalent causes of seasonal allergic

rhinitis with or without conjunctivitis (AR/C) in North America; the US National Health and Nutrition Examination Survey III (NHANES III) estimated that approximately 26% of the US population aged

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6 to 59 years are sensitized to short ragweed.<sup>1</sup> Short ragweed has been found to be partially or completely cross-reactive with all other ragweed species and sages and may cross-react with mugwort.<sup>2–5</sup> Although native to North America, ragweed has also extended its range into Europe, Asia, and Australia, and high rates of sensitization are now seen in many countries.<sup>6,7</sup>

To provide relief of AR/C symptoms, many patients rely on medications that do not have the potential of an immune-modulating effect on the underlying allergy.<sup>8</sup> Throughout most of the history of allergy immunotherapy, treatments were administered exclusively through injection, which remains the standard modality in North America.<sup>9</sup> Injection therapy requires physician-monitored dose up- and down-titration to minimize the risk of severe systemic allergic reactions.<sup>8</sup> The necessary frequent visits to a physician's office may discourage some patients from this treatment. Evidence from clinical trials suggests that sublingual tablet treatments may be associated with a relatively benign adverse event (AE) profile.<sup>9–13</sup> This may translate into a safety advantage in clinical practice by permitting patients to treat at home after the first dose has been administered and observed to be tolerated under medical supervision. As shown for subcutaneous immunotherapy, the allergen immunotherapy tablets (AIT) may modulate the immune system to induce a disease-modifying effect and therefore has the potential to prevent or reduce all manifestations of the allergic disease.<sup>12</sup> Building on this paradigm, ragweed AIT is being investigated as a novel oral treatment option for patients with ragweed-induced AR/C. In this study, the optimal clinically effective maintenance dose was to be assessed by evaluating the efficacy and long-term safety characteristics of 6- and 12-Amb a 1 unit doses of ragweed AIT.

## Methods

### Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study ([clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00783198); 67 centers were initiated in the United States, and 13 were initiated in Canada. The study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. The protocol was approved by institutional review boards for each center, and all patients gave written informed consent before any study activity.

After informed consent was obtained, each patient was screened. Patients who continued to qualify for the study were randomized in a 1:1:1 ratio according to a computer-generated randomization schedule. Patients were to receive placebo or standardized short ragweed AIT (MK-3641; Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey) of either 6 or 12 Amb a 1 units (Food and Drug Administration reference units; 1 Amb a 1 unit equals 1  $\mu$ g of the major allergen of the short ragweed *A. artemisiifolia*). The dose selection for this study was based on a previous tolerability and safety study<sup>13</sup> in which ragweed AIT doses up to and including 12 Amb a 1 units once daily were well tolerated in patients with ragweed-pollen-induced AR/C. The tablets were supplied as fast-dissolving, neutral-tasting oral lyophilisates for sublingual administration. Excipients included gelatin, mannitol, and sodium hydroxide. Placebo was indistinguishable from the active tablet in packaging, appearance, smell, and taste but contained no ragweed pollen extract. Randomization was stratified by study site and asthmatic status of the patient (yes/no). Patients were treated once daily with placebo or short ragweed AIT 6 or 12 Amb a 1 units approximately 12 weeks before and during the entire ragweed season and thereafter, for a total treatment period of 52 weeks (eFig 1).

During ragweed season, patients in all treatment groups had access to predefined, open-label allergy rescue medications, including oral and ocular antihistamines and intranasal and oral

steroids, to use in a stepwise manner if a prespecified AR/C symptom threshold was met (eFig 2). The first 3 doses of investigational medication or placebo were administered at the study site, with patients monitored for 30 minutes after dosing for adverse events; subsequent doses were self-administered at home. As a precaution, each patient was supplied with self-injectable epinephrine to be used in the event of an acute severe systemic allergic reaction.

### Study Participants

Patients eligible for inclusion in the study were 18 to 50 years of age, were of either sex, had a physician-diagnosed history of ragweed pollen-induced AR/C of 2 years' duration or longer with or without asthma, and had received treatment for their AR/C during the previous ragweed pollen season. At screening, patients were required to meet the following criteria: positive skin prick test result to *A. artemisiifolia* at screening ( $\geq 5$  mm wheal compared with saline control), positive for specific IgE against *A. artemisiifolia* (IgE class 2 or higher;  $\geq 0.7$  kU/L), and a forced expiratory volume in 1 second of 70% or higher of the predicted value at screening. Additional inclusion criteria are given in the eSupplement.

Reasons for exclusion from the trial included requiring regular medication for symptomatic seasonal or perennial allergic rhinitis and/or asthma due to another allergen during or potentially overlapping ragweed season, previous immunotherapy with ragweed or other allergen within the last 5 years, and severe asthma or asthma requiring medium- or high-dose inhaled corticosteroids. Additional exclusion criteria are presented in the eSupplement.

### Ragweed Pollen Season

Ragweed season was defined as beginning on the first day of 3 consecutive recorded days with pollen counts of 10 grains/m<sup>3</sup> or higher and ending on the last day of the last occurrence of 3 consecutive days with pollen counts of 10 grains/m<sup>3</sup> or higher. Peak season was defined as the 15 consecutive recorded days within ragweed season with the highest 15-day moving average pollen count for each site.

### Clinical Efficacy Assessments

The primary end point of the study was the total combined score (TCS), which is the sum of the rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged during peak ragweed season. Key secondary end points were the mean rhinoconjunctivitis TCS during the entire ragweed season, the mean rhinoconjunctivitis DSS during peak ragweed season, mean rhinoconjunctivitis DSS during the entire ragweed season, and the mean rhinoconjunctivitis DMS during peak ragweed season; additional secondary end points included rhinoconjunctivitis DMS during the entire ragweed season and symptoms measured by visual analogue scale (VAS) during the peak and entire ragweed season. Rhinoconjunctivitis symptom scores were recorded once daily in an electronic diary from the time of randomization through the end of the ragweed season. The rhinoconjunctivitis DSS comprises 6 symptoms measured from 0 (no symptoms) to 3 (severe symptoms) (eFig 2). The rhinoconjunctivitis DMS was composed of the sum of weighted scores for use of oral antihistamine, ocular antihistamine, nasal corticosteroid, and oral steroid (eFig 2). Symptoms were also measured by the VAS score: overall severity of rhinoconjunctivitis symptoms was recorded daily in the evening by patients, indicating a point on a line between no symptoms (0) and severe symptoms (100).

Blood samples were drawn to investigate levels of specific IgE and specific IgG4 against *A. artemisiifolia*. The serum was analyzed by ALK (Hørsholm, Denmark) and measured using the ImmunoCAP specific *A. artemisiifolia* IgE and IgG4 in serum samples. IgE and IgG4 values were log<sub>10</sub>-transformed to obtain approximately normal

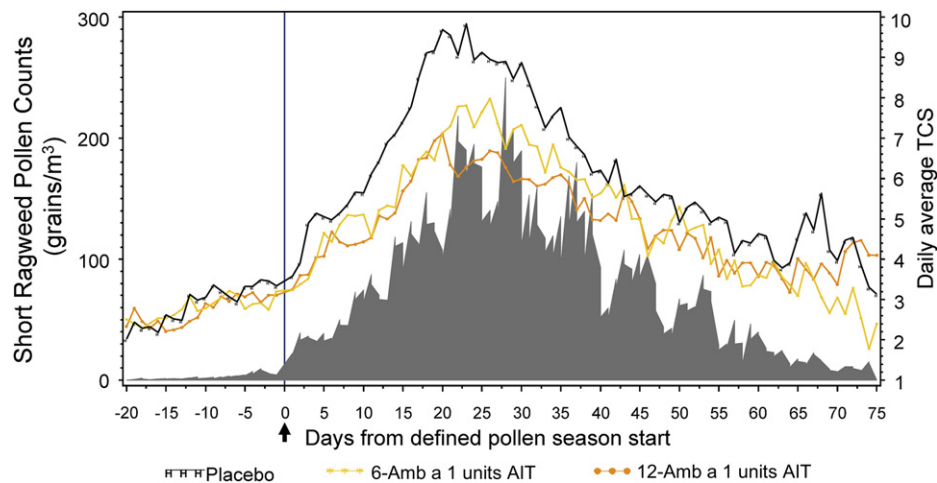


**Figure 1.** Total combined score (TCS) plotted against pollen count. AIT indicates allergy immunotherapy tablet.

distributions; all statistical analyses of immunologic parameters were performed on log<sub>10</sub>-transformed data.

Safety variables assessed included AEs, vital signs, lung function, physical examination findings, and safety laboratory assessments and were summarized by treatment groups. Severity of AEs was graded as mild (awareness of sign, symptom, or event but easily tolerated), moderate (discomfort enough to cause interference with usual activity; may warrant intervention), severe (incapacitating, with inability to do usual activities or significantly affects clinical status; warrants intervention), or life-threatening (immediate risk of death). Serious AEs were those that resulted in death; were life-threatening, resulted in persistent or significant disability or incapacity, or resulted in or prolonged an existing inpatient hospitalization; or were a congenital anomaly or birth defect in offspring of a patient receiving the study drug.

#### Statistical Analysis

On the basis of the primary efficacy end point of mean TCS during the peak ragweed season, with approximately 200 patients per group, the study was planned to be able to detect a difference of  $-1.80$  (25%) in the primary end point between an active dose group and the placebo group, with 90% power at a .05 level of significance (2-sided test).

The statistical analyses of the efficacy measurements were performed using an analysis of variance model with asthmatic condition (yes/no) and pollen region as covariates and treatment group as a fixed effect. All reported *P* values and confidence intervals (CIs) were 2-sided. Multiplicity of statistical testing on the primary and key secondary end points and multiple doses was controlled using a stepwise method, starting from the comparison of the high dose of AIT treatment vs placebo, followed by the low dose on the ordered end points from primary to key secondary in a sequential manner, as determined in the statistical analysis plan. Patients who took at least 1 dose of study medication and who had at least 1 postrandomization diary record were included in the efficacy analysis; safety analysis was based on all patients as treated (all randomized patients who received at least 1 dose of study medication). The software used for statistical analysis was SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) in Windows XP (Microsoft Corp, Redmond, Washington).

Planned subgroup analyses included descriptive summary statistics for the primary efficacy end point (mean TCS during the peak ragweed season) provided for subgroups, including those with or without local application-site reaction. Additional

information on the study methods regarding masking is in the [eSupplement](#).

## Results

### Demographic and Baseline Characteristics

Treatment groups had similar characteristics at randomization ([eTable 1](#)), with 85% of patients being sensitized to multiple allergens in addition to ragweed and other weeds and approximately 20% having asthma. Between September 25, 2009, and May 13, 2010, a total of 1,164 potential study participants were screened; principal reasons for screening failure were specific IgE or skin prick test results that did not meet the inclusion criteria. A total of 565 patients were randomized across the study's 80 sites and received at least one dose of study medication. Patient disposition (all randomized patients) is shown in [eFigure 3](#). Five patients from one site were excluded from all efficacy analyses because of the site's conflicts with good clinical practice; no AEs were reported among the patients at this site. A total of 423 randomized patients (74.9%) completed the protocol-specified, double-blind treatment period, whereas 142 patients (25.1%) discontinued the investigational treatment early. The primary reasons for study discontinuation were not wishing to continue for reasons unrelated to assigned study treatment (56 patients, 9.9% overall) and AEs (37 patients, 6.5% overall). No patients discontinued the trial because of treatment failure. The study ended on the last patient's last visit on May 23, 2011.

### Ragweed Pollen Season

The mean ragweed season lasted approximately 44 days, and the weighted (by number of patients exposed) mean pollen count per day during the season was 122 grains/m<sup>3</sup>. The weighted mean pollen count per day during the peak season was 204 grains/m<sup>3</sup>.

### Efficacy Findings

Overall, a dose-dependent treatment response was observed, with the 12-Amb a 1 unit AIT dose showing a greater separation from placebo compared with the 6-Amb a 1 unit AIT dose for the TCS, DMS, and DSS measurements. Significant treatment differences from placebo in these efficacy measures were of a similar absolute magnitude during the peak and entire ragweed season for both active doses.

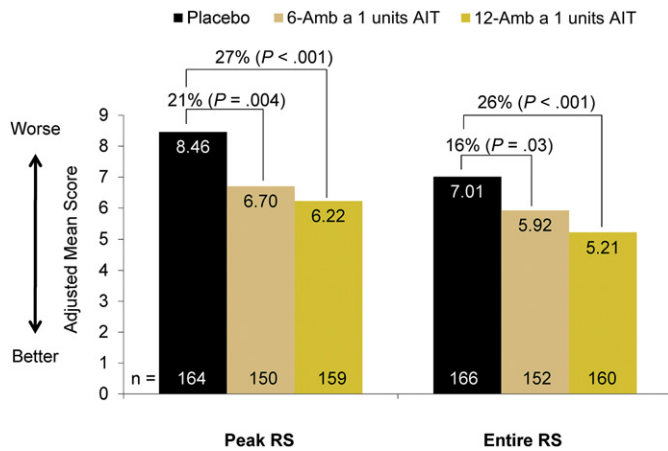


**Figure 2.** Total combined score during the peak and entire ragweed season (RS). Treatment differences vs placebo over peak RS were  $-1.76$  (95% confidence interval [CI],  $-2.95$  to  $-0.57$ ) for the 6–Amb a 1 unit dose and  $-2.24$  (95% CI,  $-3.41$  to  $-1.07$ ) for the 12–Amb a 1 unit dose. Treatment differences vs placebo over the entire RS were  $-1.09$  (95% CI,  $-2.08$  to  $-0.09$ ) for the 6–Amb a 1 unit dose and  $-1.80$  (95% CI,  $-2.78$  to  $-0.82$ ) for the 12–Amb a 1 unit dose. AIT indicates allergy immunotherapy tablet.

#### Daily TCS

The TCS for each treatment group is plotted against the daily mean pollen count in Figure 1. The change in TCS paralleled mean pollen counts during the entire ragweed season. During the peak ragweed season, the ragweed AIT 6–Amb a 1 unit and 12–Amb a 1 unit groups had 21% (difference,  $-1.76$  score point;  $P = .004$ ) and 27% (difference,  $-2.24$  score point;  $P < .001$ ) respective reductions in TCS compared with the placebo group (Fig 2). During the entire ragweed season, the 6–Amb a 1 unit and 12–Amb a 1 unit groups had 16% (difference,  $-1.09$  score point;  $P = .03$ ) and 26% (difference,  $-1.80$  score point;  $P < .001$ ) respective reductions in TCS compared with the placebo group (Fig 2).

#### Daily Medication Score

During the peak ragweed season, when patients had the most symptoms and rescue medications are expected to be most used, the 6–Amb a 1 unit and 12–Amb a 1 unit ragweed AIT doses yielded significant 34% and 45% ( $P < .05$ ) respective reductions in DMS compared with placebo (Table 1). During the entire ragweed season, the 6–Amb a 1 unit and 12–Amb a 1 unit ragweed AIT doses yielded 29% and 46% ( $P < .05$ ) respective reductions in DMS compared with placebo.

**Table 1**  
DMS, DSS, and VAS scores during the peak and entire ragweed season

| Scale                          | Peak season          |                                           |                                            | Entire season        |                                           |                                            |
|--------------------------------|----------------------|-------------------------------------------|--------------------------------------------|----------------------|-------------------------------------------|--------------------------------------------|
|                                | Placebo<br>(n = 164) | Ragweed AIT, 6 Amb<br>a 1 units (n = 150) | Ragweed AIT, 12 Amb<br>a 1 units (n = 159) | Placebo<br>(n = 166) | Ragweed AIT, 6 Amb<br>a 1 units (n = 152) | Ragweed AIT, 12 Amb<br>a 1 units (n = 160) |
| DMS                            | 2.87                 | 1.89                                      | 1.57                                       | 2.15                 | 1.52                                      | 1.16                                       |
| Difference vs placebo (95% CI) |                      | $-0.98$ ( $-1.65$ to $-0.32$ )            | $-1.30$ ( $-1.95$ to $-0.64$ )             |                      | $-0.63$ ( $-1.18$ to $-0.08$ )            | $-0.98$ ( $-1.53$ to $-0.44$ )             |
| P                              |                      | .004                                      | <.001                                      |                      | .02                                       | <.001                                      |
| Reduction vs placebo, %        |                      | 34                                        | 45                                         |                      | 29                                        | 46                                         |
| DSS                            | 5.59                 | 4.81                                      | 4.65                                       | 4.87                 | 4.41                                      | 4.05                                       |
| Difference vs placebo (95% CI) |                      | $-0.78$ ( $-1.54$ to $-0.01$ )            | $-0.94$ ( $-1.70$ to $-0.19$ )             |                      | $-0.46$ ( $-1.11$ to $0.19$ )             | $-0.82$ ( $-1.46$ to $-0.18$ )             |
| P                              |                      | .047                                      | .01                                        |                      | .17                                       | .01                                        |
| Reduction vs placebo, %        |                      | 14                                        | 17                                         |                      | 9                                         | 17                                         |
| VAS score                      | 26.36                | 24.89                                     | 19.98                                      | 22.92                | 23.02                                     | 17.27                                      |
| Difference vs placebo (95% CI) |                      | $-1.48$ ( $-6.30$ to $3.35$ )             | $-6.38$ ( $-11.14$ to $-1.63$ )            |                      | 0.10 ( $-4.18$ to $4.37$ )                | $-5.65$ ( $-9.87$ to $-1.43$ )             |
| P                              |                      | .55                                       | .009                                       |                      | .97                                       | .009                                       |
| Reduction vs placebo, %        |                      | 6                                         | 24                                         |                      | 0                                         | 25                                         |

Abbreviations: AIT, allergy immunotherapy tablet; DMS, daily medication score; DSS, daily symptom score; VAS, visual analogue scale.

Between-group differences in rates of rescue medication use were summarized with descriptive statistics. Figure 3 shows percentages of patients in all groups who used the various rescue medications during the 15-day peak ragweed season. During the entire ragweed season, loratadine was used by 66.9%, 52.6%, and 48.1% of patients in the placebo, 6–Amb a 1 unit, and 12–Amb a 1 unit groups; olopatadine was used by 25.9%, 19.1%, and 18.8%, respectively; and mometasone was used by 35.5%, 27.6%, and 19.4%, respectively. No patients used prednisone during peak or entire ragweed season.

#### Daily Symptom Score

During the peak ragweed season, the 6–Amb a 1 unit and 12–Amb a 1 unit ragweed AIT doses yielded significant reductions in DSS compared with placebo (14% and 17%, respectively;  $P < .05$ ) (Table 1). During the entire ragweed season, the DSS for the 6–Amb a 1 unit AIT dose showed numeric reduction (9%;  $P = .17$ ), whereas the DSS for the 12–Amb a 1 unit AIT dose showed significant superiority to placebo (17%;  $P = .01$ ) in ability to reduce the symptoms of AR/C.

#### VAS Score

The symptomatic advantages seen for ragweed AIT in DSS were also reflected by corresponding reductions in AR/C symptoms via VAS scores. During the peak ragweed season, the VAS scores in the 6–Amb a 1 unit group were numerically lower (6%) than in the placebo group, whereas the VAS scores in the 12–Amb a 1 unit group were significantly lower (24%;  $P = .009$ ) than placebo, indicating reduction in symptom burden (Table 1). During the entire ragweed season, the VAS for the 6–Amb a 1 unit group showed no reduction vs placebo, whereas the VAS for the 12–Amb a 1 unit group demonstrated significant 25% ( $P = .009$ ) symptom reduction vs placebo.

#### Immunologic Parameters

A *artemisiifolia* specific IgE and IgG4 values at baseline were similar among treatment groups. A *artemisiifolia* specific IgG4 and IgE levels and log<sub>10</sub>-normalized levels in the ragweed AIT treatment groups increased over time after initiation of treatment, whereas the corresponding levels in the placebo group remained constant ( $P < .001$  for log<sub>10</sub> normalized levels in each AIT group vs placebo at each time point [data not shown]).

#### Subgroup Analyses

In planned exploratory analyses, numerical advantages in TCS over the peak ragweed season were seen for both ragweed AIT

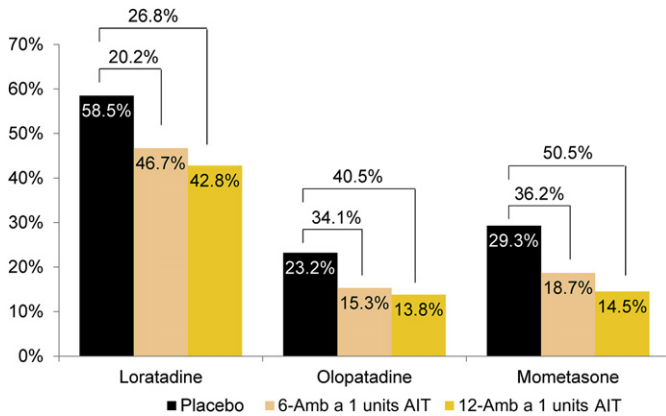


**Figure 3.** Percentages of patients reporting rescue medication use during peak ragweed season. Values above lines between columns indicate percentage difference vs placebo. AIT, allergy immunotherapy tablet; RS, ragweed pollen season. Difference in rates of rescue medication use between groups were summarized with descriptive statistics only and no assessment of statistical significance was made.

doses vs placebo in subgroups according to sex, race, asthma, geographic region, allergen sensitization type, and preseason treatment duration (data not shown). Among 284 patients without local application-site reactions in this study, the TCS was reduced vs placebo by 36% (−3.12; 95% CI, −4.75 to −1.48) and 25% (−2.16; 95% CI, −3.86 to −0.47) for the 6–Amb a 1 unit and 12–Amb a 1 unit groups, respectively, during peak ragweed season. By comparison, among the 189 patients with local application-site reactions, 6 and 12 Amb a 1 units of ragweed AIT were associated with reductions in peak-season TCS of 5% (−0.46; 95% CI, −2.93 to 2.02) and 21% (−1.76; 95% CI, −4.01 to 0.49), respectively, vs placebo. No analyses of statistical significance were conducted of treatment effect in these subgroups.

### Safety

Treatment with ragweed AIT was well tolerated, with no deaths, systemic allergic reactions, or life-threatening events. The most frequently reported treatment-related AEs (TRAEs) were local application-site reactions of the mouth, throat, and ear (primarily oral pruritus, throat irritation, swollen tongue, and ear pruritus)

**Table 2**  
Treatment-related treatment-emergent AEs occurring in 2% of patients or more<sup>a</sup>

| AE                | Patients, %          |                                           |                                            |
|-------------------|----------------------|-------------------------------------------|--------------------------------------------|
|                   | Placebo<br>(n = 188) | Ragweed AIT, 6 Amb<br>a 1 units (n = 190) | Ragweed AIT, 12 Amb<br>a 1 units (n = 187) |
| Any AE            | 28.2                 | 58.9                                      | 68.4                                       |
| Ear pruritus      | 2.1                  | 15.8                                      | 16.0                                       |
| Eye pruritus      | 0.5                  | 4.2                                       | 4.3                                        |
| Lip swelling      | 1.6                  | 3.2                                       | 7.5                                        |
| Nausea            | 0.5                  | 2.1                                       | 3.7                                        |
| Oral pruritus     | 3.2                  | 18.4                                      | 19.2                                       |
| Oral paraesthesia | 2.1                  | 7.4                                       | 10.7                                       |
| Swollen tongue    | 3.2                  | 11.6                                      | 19.3                                       |
| Tongue edema      | 0.5                  | 2.1                                       | 4.3                                        |
| Tongue pruritus   | 1.6                  | 16.8                                      | 14.4                                       |
| Cough             | 0.0                  | 2.6                                       | 4.3                                        |
| Dry throat        | 0.5                  | 4.7                                       | 2.1                                        |
| Pharyngeal edema  | 1.1                  | 3.7                                       | 4.8                                        |
| Throat irritation | 5.3                  | 25.3                                      | 28.9                                       |
| Pruritus          | 0.0                  | 6.3                                       | 4.8                                        |

Abbreviations: AE, adverse event; AIT, allergy immunotherapy tablet.

<sup>a</sup>Treatment-emergent AE was defined as a new or worsening AE reported on or after treatment start date through treatment stop date plus 30 days; relationship to treatment was assessed by the investigator.

(Table 2). These TRAEs were generally early occurring, and self-resolving; most local application-site reactions occurred within the first week of treatment and were experienced during the first weeks of treatment (eTable 2). The 5 most frequently occurring local application-site TRAEs (oral paraesthesia, ear pruritus, swollen tongue, oral pruritus, and throat irritation) tended to first occur within the first few days of treatment, and the median number of consecutive days each occurred was less than 7. Allergic conjunctivitis was experienced as a treatment-emergent (new or worsening after beginning of treatment) AE by 6 patients, seasonal allergy by 1, and allergic rhinitis by 6.

Most patients (>82%) experiencing treatment-emergent AEs had their AEs assessed as mild or moderate. Severe TRAEs were experienced by 1 (0.5%), 9 (4.7%), and 11 (5.9%) patients in the placebo, 6–Amb a 1 unit AIT, and 12–Amb a 1 unit AIT arms, respectively. There were 3 (1.6%), 15 (7.9%), and 19 (10.2%) patients in the placebo, 6–Amb a 1 unit AIT, and 12–Amb a 1 unit groups, respectively, who experienced treatment-emergent AEs that led to discontinuation; of these, 0, 3, and 6 patients discontinued because of severe AEs. Severe local application-site TRAEs were experienced by 0, 3 (1.6%), and 7 (3.7%) patients receiving placebo, 6–Amb a 1 unit AIT, and 12–Amb a 1 unit AIT, respectively. There were 0, 9 (4.7%), and 12 (6.4%) patients in the placebo, 6–Amb a 1 unit AIT, and 12–Amb a 1 unit AIT groups, respectively, who experienced treatment-emergent local application-site AEs that led discontinuation; of these, 0, 1, and 4 patients discontinued because of severe local application-site AEs. These events were not rapidly progressing and did not lead to more concerning manifestations, such as airway obstruction. There were no serious TRAEs.

Two patients received epinephrine during the study. One patient in the 6–Amb a 1 unit group reported severe pharyngeal edema on day 22 of treatment, which occurred within 1 minute of dosing. The patient had local events, which may have been progressing in severity before this severe event. The patient transported herself to an emergency facility and received treatment with diphenhydramine, methylprednisolone, and epinephrine. It is of note that there was no objective swelling apparent on physical examination at admission. The differential diagnosis from the emergency department reported allergic reaction vs anxiety. However, on discharge, the physician note indicated that the event was a possible allergic reaction. The event was considered likely related to study treatment, and the patient discontinued the study. One patient in the 12–Amb a 1 unit AIT arm with a known history of food allergy used epinephrine because of an unrelated adverse reaction to nuts; the event was considered unrelated to treatment, and the patient completed the study.

Safety findings were similar between asthmatic and non-asthmatic patients, and no new safety signals emerged.

### Discussion

The results of this trial indicate that ragweed AIT is associated with significant reductions in symptoms and rescue medication use vs placebo when measured by changes in TCS, DMS, DSS, and VAS score. Further, the efficacy of the single AIT was seen in a largely polysensitized population. Although the safety profiles of the 6– and 12–Amb a 1 unit doses were similar in this study, a more pronounced clinical efficacy effect was noted with the 12–Amb a 1 unit dose. The greater efficacy of the 12–Amb a 1 unit dose for the primary and key secondary end points was further confirmed by significant improvement in symptoms as revealed by the VAS. A reduction in the need for symptomatic allergy medication was also revealed during ragweed season, with the decrease in need for topical nasal corticosteroids being largest for the 12–Amb a 1 unit dose. The long-term safety results indicated most AEs to be self-limiting, mild or moderate local application-site reactions, with

no systemic allergic events observed in the study. This relatively benign safety profile is in line with previous safety assessments of sublingual immunotherapy and suggests that sublingual ragweed tablet therapy may be safe for self-administration of immunotherapy at home. To date, there are no reports of deaths and fewer than 20 reported instances of severe anaphylaxis associated with the approximately 1 billion sublingual immunotherapy doses administered worldwide since 2000.<sup>14</sup>

The existing clinical evidence for sublingual immunotherapy of ragweed pollen-induced AR/C is limited. There are only 3 relatively small (approximately 100 patients) randomized, placebo-controlled trials using drop-based formulations; in 2, sublingual treatment failed to show significant improvement vs placebo in symptom or medication scores, whereas in the third study significant advantages were seen for the high (48 µg of Amb a 1 daily) dose of drops after symptom and medication scores were adjusted for baseline symptoms.<sup>15–17</sup> The placebo-controlled trial literature that validated the efficacy of subcutaneous immunotherapy for ragweed allergy was a series of single-center studies conducted in the 1960s and 1970s, before today's rescue medication options were available.<sup>18–20</sup> Although subsequent research introduced refinements in trial design,<sup>21–23</sup> there exists no evaluation of subcutaneous immunotherapy for ragweed allergy comparable to the present large multicenter study.

The present study is limited in that it investigated 1 year of ragweed AIT treatment while full courses of immunotherapy are typically performed during several years. In a clinical trial conducted in European patients, Timothy grass AIT was found to have a disease-modifying effect; in long-term follow-up results, patients who had received 3 years of treatment with grass AIT had significantly lower symptom and medication scores vs patients who had received placebo, even 2 years after end of treatment.<sup>12</sup> On the basis of the same symptom scale as was used in our study, patients who had received grass AIT had a 25% reduction in symptoms vs those who had received placebo in the second-year posttreatment follow-up.<sup>12</sup> Notably, the duration of treatment used to achieve this disease-modifying effect was consistent with the duration of treatment that appears to be necessary to achieve disease modification with subcutaneous allergy immunotherapy.<sup>24–26</sup> An additional limitation is that the present study was conducted only in North America, whereas ragweed is rapidly becoming a dominant pollen allergen worldwide.<sup>6,7</sup> A trial of ragweed AIT has recently been conducted in North America and Europe, with findings of similar efficacy to that in the present trial.<sup>27</sup> Finally, it has been suggested previously that trials of AIT are limited by bias because the prevalent local application-site reactions could compromise blinding.<sup>28</sup> However, in a predefined subgroup analysis, among 284 patients without local site reactions in this study, the TCS was reduced vs placebo by 36% (–3.12; 95% CI, –4.75 to –1.48) and 25% (–2.16; 95% CI, –3.86 to –0.47) for the 6–Amb a 1 unit and 12–Amb a 1 unit groups, respectively, during peak ragweed season. This finding suggests a treatment effect was seen even without the possible unblinding via local application-site reactions.

In conclusion, the continued spread of ragweed and its associated allergic burden underscore the need for effective immunotherapy options for patients who are unwilling to undergo injection therapy. The results of this trial replicate those from another pivotal ragweed AIT efficacy and safety study<sup>27</sup> and corroborate its findings that ragweed AIT is effective, is well tolerated, and may provide a new convenient treatment modality for North American patients with ragweed-induced AR/C.

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## Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2013.03.013>.

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**eSupplement**

## Additional inclusion criteria:

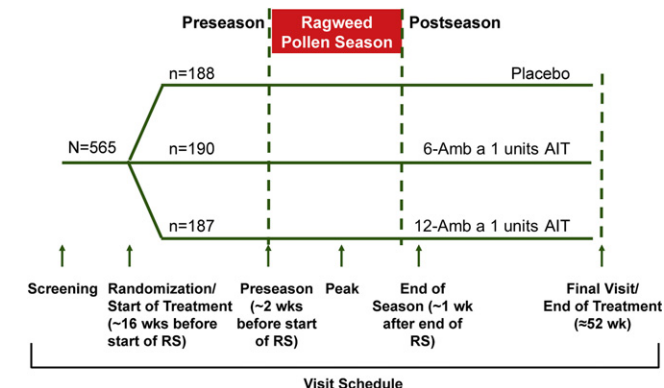
Patients' safety laboratory test results and vital signs at screening had to be within normal limits or clinically acceptable to the investigator or sponsor. Patients had to have been willing to give informed written consent and be able to adhere to dose and visit schedules, and female patients of childbearing potential were required to use an acceptable form of birth control, to be counseled in its appropriate use, and to provide a negative pregnancy test result at screening.

## Additional exclusion criteria:

In addition, any patient who was a female and was breast-feeding, was pregnant, or intended to become pregnant; who had history of allergy, hypersensitivity, or intolerance to the ingredients of the rescue medications, self-injectable epinephrine, or allergen immunotherapy tablet (except for *A. artemisiifolia*); who had received immunosuppressive treatment within the past 3 months (except steroids for allergic or asthma symptoms); who had severe atopic dermatitis; who had history of anaphylaxis with cardiorespiratory symptoms, chronic urticaria and angioedema, chronic sinusitis within the past 2 years, or self-injectable epinephrine use; who had any clinically significant condition or situation that the investigator judged would interfere with participation or study

evaluations; who had used any investigational drugs within 30 days of screening; who was participating in any other clinical trial; who was a family member of the investigational study staff; who was unable to meet medication washout requirements; who was unlikely to be able to complete the trial or likely to travel for extended periods during the season; who had any clinically significant abnormal vital sign or laboratory value; or who was unable to or would not comply with the use of self-injectable epinephrine or was at a greater risk of developing adverse reactions after its use was ineligible. Patients could not have participated in the same study at another site or have been randomized more than once.

Patients were enrolled by the investigator or qualified representative. Randomization was conducted by an external randomization group using an interactive voice response system. The sponsor created 2 sets of randomization schedules: one for patient randomization numbers and the other for kit numbers; randomization was stratified by study site and asthma status. Treatments were provided in identical packaging numbered according to the randomization schedule; the sponsor, patients, investigators, and study personnel were masked to treatment. Masking was maintained until database lock. No interim analyses were planned.



**eFigure 1.** Study design. AIT indicates allergy immunotherapy tablet; RS, ragweed season.

| Subjects (N=565)                 |            |                                  |            |
|----------------------------------|------------|----------------------------------|------------|
| Placebo                          |            | Ragweed AIT<br>6 Amb a 1 units   |            |
|                                  | n (%)      |                                  | n (%)      |
| Randomized                       | 188 (100)  | Randomized                       | 190 (100)  |
| Treated                          | 188 (100)  | Treated                          | 190 (100)  |
| Discontinued                     | 42 (22.3)  | Discontinued                     | 57 (30.0)  |
| AE                               | 3 (1.6)    | AE                               | 15 (7.9)   |
| Lost to Follow-up                | 7 (3.7)    | Lost to Follow-up                | 11 (5.8)   |
| Subject Withdrawal               | 20 (10.6)  | Subject Withdrawal               | 22 (11.6)  |
| Noncompliance                    | 10 (5.3)   | Noncompliance                    | 7 (3.7)    |
| Site excluded                    | 2 (1.1)    | Site excluded                    | 2 (1.1)    |
| Included in TCS/DSS/DMS (peak)   | 164 (87.2) | Included in TCS/DSS/DMS (peak)   | 150 (78.9) |
| Included in TCS/DSS/DMS (entire) | 166 (88.3) | Included in TCS/DSS/DMS (entire) | 152 (80.0) |
| Completed                        | 146 (77.7) | Completed                        | 133 (70.0) |

| Ragweed AIT<br>12 Amb a 1 units  |            |
|----------------------------------|------------|
|                                  | n (%)      |
| Randomized                       | 187 (100)  |
| Treated                          | 187 (100)  |
| Discontinued*                    | 43 (23.0)  |
| AE                               | 19 (10.2)  |
| Lost to Follow-up                | 1 (0.5)    |
| Subject Withdrawal               | 14 (7.5)   |
| Noncompliance                    | 7 (3.7)    |
| Site excluded                    | 1 (0.5)    |
| Included in TCS/DSS/DMS (peak)   | 159 (85.0) |
| Included in TCS/DSS/DMS (entire) | 160 (85.6) |
| Completed                        | 144 (77.0) |

**eFigure 3.** Disposition of study patients. \*One patient in the 12–Amb a 1 unit group received at least 1 dose of study medication but had no postrandomization efficacy measurement. AE indicates adverse event; AIT, allergy immunotherapy tablet; DMS, daily medication score; DSS, daily symptom score; TCS, total combined score. Some patients discontinued after providing diary entry during ragweed season and thus are included in both the discontinued set and efficacy evaluations.

| DSS, Maximum=18 |                   |  |                                                                                                                        |
|-----------------|-------------------|--|------------------------------------------------------------------------------------------------------------------------|
| 0               | No symptoms       |  | Individual symptoms:<br>▪ runny nose<br>▪ blocked nose<br>▪ sneezing<br>▪ itchy nose<br>▪ gritty eyes<br>▪ watery eyes |
| 1               | Mild symptoms     |  |                                                                                                                        |
| 2               | Moderate symptoms |  |                                                                                                                        |
| 3               | Severe symptoms   |  |                                                                                                                        |

| DMS, Maximum=36                                                                                 |                                                                                                        |                       |                     |
|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------|---------------------|
| Rescue Medication                                                                               | Requirements for Start of Use                                                                          | Score/Dose Unit       | Maximum Daily Score |
| Oral antihistamine <sup>a</sup> 10-mg tablet: 1 tablet QD                                       | Total symptom score ≥4 and start of RS confirmed by site                                               | 6 points/tablet       | 6                   |
| Ocular antihistamine <sup>b</sup> HCl 0.1% ophthalmic solution - 1 drop in the affected eye BID | Addition to loratadine for persistent eye symptoms                                                     | 1.5 points/drop       | 6                   |
| Nasal steroid <sup>c</sup> nasal spray 50 µg - 2 sprays in each nostril QD                      | Total symptom score ≥4 despite loratadine. Use in addition to loratadine                               | 2 points/spray        | 8                   |
| Oral steroid <sup>d</sup> 5-mg tablet (Day 1 - 1 mg/kg/day, max 50 mg/day)                      | Total symptom score ≥4 despite loratadine and mometasone. Use in addition to loratadine and mometasone | 1.6 points/tablet     | 16                  |
| Oral steroid <sup>d</sup> 5-mg tablet (Day 2+ - 0.5 mg/kg/day, max 25 mg/day)                   |                                                                                                        | 1.6 points x 2/tablet | 16                  |

**eFigure 2.** Symptom and medication scoring. <sup>a</sup>Loratadine (Claritin; Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey); <sup>b</sup>olopatadine (Patanol; Alcon, Hünenberg, Switzerland); <sup>c</sup>mometasone furoate (Nasonex; Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey); <sup>d</sup>prednisone (West-Ward Pharmaceuticals, Lionville, Pennsylvania). DMS indicates daily medication score; DSS, daily symptom score; RS, ragweed season.

**eTable 1**  
Demographics and baseline characteristics

| Characteristic                                            | Placebo (n = 188) | Ragweed AIT, 6 Amb a 1 units (n = 190) | Ragweed AIT, 12 Amb a 1 units (n = 187) |
|-----------------------------------------------------------|-------------------|----------------------------------------|-----------------------------------------|
| Female, No. (%)                                           | 93 (50)           | 84 (44)                                | 109 (58)                                |
| Age, mean (range), y                                      | 35.9 (18–50)      | 35.3 (18–50)                           | 34.9 (18–51)                            |
| White race, No. (%)                                       | 139 (74)          | 151 (80)                               | 153 (82)                                |
| Asthmatic, No. (%)                                        | 43 (23)           | 37 (20)                                | 42 (23)                                 |
| Duration of ragweed allergy, y                            | 19                | 19                                     | 19                                      |
| Mean (SD) wheal measurement, mm                           |                   |                                        |                                         |
| Histamine                                                 | 6.3 (2.3)         | 6.2 (2.2)                              | 6.3 (2.0)                               |
| Saline                                                    | 0.4 (0.8)         | 0.4 (1.0)                              | 0.5 (1.0)                               |
| <i>Ambrosia artemisiifolia</i> extract                    | 11.3 (4.3)        | 11.7 (4.4)                             | 11.3 (3.9)                              |
| Ragweed specific IgE, mean (SD), kU/L                     | 16.4 (20.7)       | 14.0 (18.2)                            | 17.5 (21.9)                             |
| Multisensitized, No. (%)                                  | 159 (85)          | 163 (86)                               | 159 (85)                                |
| Sensitized to other than weed allergens (specific IgE), % |                   |                                        |                                         |
| Tree                                                      | 60                | 56                                     | 61                                      |
| Grass                                                     | 55                | 53                                     | 49                                      |
| Mold <sup>a</sup>                                         | 8                 | 8                                      | 9                                       |
| <i>Alternaria tenuis</i>                                  | 27                | 24                                     | 22                                      |
| Cat                                                       | 44                | 45                                     | 45                                      |
| Dog                                                       | 36                | 35                                     | 39                                      |
| <i>Dermatophagoides farinae</i> mite                      | 39                | 34                                     | 45                                      |
| <i>Dermatophagoides pteronyssinus</i> mite                | 38                | 35                                     | 45                                      |
| Preseason duration <12 weeks, No. (%)                     | 12 (6)            | 33 (17)                                | 24 (13)                                 |
| Preseason duration ≥12 weeks to <16 weeks, No. (%)        | 28 (15)           | 26 (14)                                | 17 (9)                                  |
| Preseason duration ≥16 weeks, No. (%)                     | 148 (79)          | 131 (69)                               | 146 (78)                                |

Abbreviation: AIT, allergy immunotherapy tablet.

<sup>a</sup>Mold panel (*Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, *Candida*, and *Helminthosporium*).

**eTable 2**

Number of patients experiencing treatment-emergent local application-site TRAEs and their onset and duration (both in days)

|                        | Onset             |                                           |                                            | Duration <sup>a</sup> |                                           |                                            |
|------------------------|-------------------|-------------------------------------------|--------------------------------------------|-----------------------|-------------------------------------------|--------------------------------------------|
|                        | Placebo (n = 188) | Ragweed AIT, 6 Amb<br>a 1 units (n = 190) | Ragweed AIT, 12 Amb<br>a 1 units (n = 187) | Placebo (n = 188)     | Ragweed AIT, 6 Amb<br>a 1 units (n = 190) | Ragweed AIT, 12 Amb<br>a 1 units (n = 187) |
| Dysphagia              |                   |                                           |                                            |                       |                                           |                                            |
| No.                    |                   | 4                                         | 5                                          |                       | 4                                         | 5                                          |
| Median (range)         |                   | 17 (9-35)                                 | 12 (12-44)                                 |                       | 1 (1)                                     | 16 (1-37)                                  |
| Ear pruritus           |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 5                 | 39                                        | 33                                         | 5                     | 39                                        | 33                                         |
| Median (range)         | 5 (2-6)           | 1 (1-119)                                 | 2 (1-23)                                   | 1 (1-2)               | 4 (1-359)                                 | 6 (1-371)                                  |
| Glossodynia            |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 2                 | 2                                         | 3                                          | 2                     | 2                                         | 3                                          |
| Median (range)         | 101 (101-101)     | 90 (47-133)                               | 12 (1-150)                                 | 8 (8)                 | 1 (1)                                     | 2 (1-334)                                  |
| Oral hypoesthesia      |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 1                 | 6                                         | 3                                          | 1                     | 6                                         | 3                                          |
| Median (range)         | 2 (2)             | 5 (1-205)                                 | 12 (2-17)                                  | 1 (1)                 | 1 (1-2)                                   | 2 (1-3)                                    |
| Lip edema              |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 1                 | 7                                         | 5                                          | 1                     | 7                                         | 5                                          |
| Median (range)         | 4 (4)             | 3 (1-118)                                 | 28 (1-146)                                 | 3 (3)                 | 1 (1-14)                                  | 2 (1-105)                                  |
| Lip swelling           |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 4                 | 10                                        | 16                                         | 4                     | 10                                        | 16                                         |
| Median (range)         | 2 (1-110)         | 14 (1-310)                                | 10 (1-262)                                 | 1 (1)                 | 1 (1-79)                                  | 1 (1-375)                                  |
| Mouth edema            |                   |                                           |                                            |                       |                                           |                                            |
| No.                    |                   | 2                                         | 1                                          |                       | 2                                         | 1                                          |
| Median (range)         | 0                 | 37 (29-44)                                | 1 (1)                                      |                       | 5 (2-7)                                   | 1 (1)                                      |
| Oral pruritus          |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 6                 | 40                                        | 44                                         | 6                     | 39                                        | 44                                         |
| Median (range)         | 3 (1-7)           | 1 (1-176)                                 | 2 (1-391)                                  | 2 (1-3)               | 2 (1-374)                                 | 4 (1-224)                                  |
| Oropharyngeal swelling |                   |                                           |                                            |                       |                                           |                                            |
| No.                    |                   |                                           | 3                                          |                       |                                           | 3                                          |
| Median (range)         |                   |                                           | 13 (3-20)                                  |                       |                                           | 8 (2-8)                                    |
| Palatal edema          |                   |                                           |                                            |                       |                                           |                                            |
| No.                    |                   | 1                                         | 8                                          |                       | 1                                         | 8                                          |
| Median (range)         |                   | 1 (1)                                     | 2 (1-11)                                   |                       | 2 (2)                                     | 2 (1-19)                                   |
| Oral paresthesia       |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 5                 | 18                                        | 28                                         | 5                     | 17                                        | 28                                         |
| Median (range)         | 1 (1-3)           | 2 (1-149)                                 | 2 (1-262)                                  | 1 (1-2)               | 1 (1-377)                                 | 2 (1-147)                                  |
| Pharyngeal edema       |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 3                 | 8                                         | 12                                         | 3                     | 8                                         | 12                                         |
| Median (range)         | 146 (1-253)       | 9 (1-25)                                  | 9 (1-156)                                  | 10 (2-106)            | 2 (1-26)                                  | 4 (1-53)                                   |
| Stomatitis             |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 1                 | 4                                         | 3                                          | 1                     | 4                                         | 2                                          |
| Median (range)         | 1 (1)             | 12 (7-159)                                | 11 (4-15)                                  | 1 (1)                 | 30 (3-109)                                | 3 (1-5)                                    |
| Facial swelling        |                   |                                           |                                            |                       |                                           |                                            |
| No.                    |                   | 1                                         |                                            |                       | 1                                         |                                            |
| Median (range)         |                   | 14 (14)                                   |                                            |                       | 9 (9)                                     |                                            |
| Swollen tongue         |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 7                 | 24                                        | 50                                         | 7                     | 23                                        | 49                                         |
| Median (range)         | 2 (1-7)           | 15 (1-267)                                | 13 (1-371)                                 | 2 (1-13)              | 3 (1-353)                                 | 2 (1-185)                                  |
| Throat irritation      |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 13                | 72                                        | 72                                         | 13                    | 72                                        | 71                                         |
| Median (range)         | 2 (1-146)         | 3 (1-300)                                 | 2 (1-128)                                  | 1 (1-13)              | 2 (1-307)                                 | 6 (1-373)                                  |
| Throat tightness       |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 2                 | 2                                         | 4                                          | 2                     | 2                                         | 4                                          |
| Median (range)         | 2 (1-2)           | 2 (2)                                     | 70 (1-137)                                 | 1 (1)                 | 1 (1)                                     | 1 (1)                                      |
| Tongue edema           |                   |                                           |                                            |                       |                                           |                                            |
| No.                    | 1                 | 7                                         | 9                                          | 1                     | 7                                         | 9                                          |
| Median (range)         | 1 (1)             | 9 (2-22)                                  | 12 (1-38)                                  | 2 (2)                 | 1 (1-11)                                  | 3 (1-106)                                  |

Abbreviations: AIT, allergy immunotherapy tablet; TRAE, treatment-related adverse event.

<sup>a</sup>Duration indicates consecutive number of days on which the TRAE occurred at any time; it does not indicate that the TRAE was constantly present.