



Contents lists available at ScienceDirect



Safety and tolerability of a short ragweed sublingual immunotherapy tablet

Hendrik Nolte, MD, PhD^{*}; Niran Amar, MD[†]; David I. Bernstein, MD[‡]; Bobby Q. Lanier, MD[§]; Peter Creticos, MD^{||}; Gary Berman, MD[¶]; Amarjot Kaur, PhD^{*}; Jacques Hébert, MD[#]; and Jennifer Maloney, MD^{*}

^{*} Merck & Co, Inc, Whitehouse Station, New Jersey

[†] Allergy & Asthma Research Institute, Waco, Texas

[‡] Bernstein Clinical Research Center and Division of Immunology and Allergy, University of Cincinnati, Cincinnati, Ohio

[§] North Texas Institute for Clinical Trials, Fort Worth, Texas

^{||} Creticos Research Group and Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, Maryland

[¶] Minneapolis Allergy & Asthma Specialists, Minneapolis, Minnesota

[#] Centre de Recherche Appliquée en Allergie de Québec, Québec, Québec, Canada

ARTICLE INFO

Article history:

Received for publication December 23, 2013.

Received in revised form April 2, 2014.

Accepted for publication April 29, 2014.

ABSTRACT

Background: MK-3641 is a short ragweed sublingual tablet under investigation for immunotherapy of ragweed pollen–induced allergic rhinitis.

Objective: To characterize the safety and tolerability of a ragweed sublingual tablet (Merck/ALK-Abelló) in ragweed-allergic adults with or without conjunctivitis.

Methods: Data from 4 randomized, double-blinded, placebo-controlled trials of MK-3641 (2 28-day and 2 52-week trials) were evaluated. Pooled analyses examined short-term safety over 28 days from all 4 trials and long-term safety from the 52-week trials.

Results: Across all studies, 757, 198, 454, and 1,058 subjects were randomized to placebo or 1.5, 6, or 12 Amb a 1-U of MK-3641, respectively. Treatment-related adverse events were more frequent in the 6- and 12-Amb a 1-U MK-3641 groups than in the placebo group and were primarily local application-site reactions occurring in the first few days of treatment. There was no treatment-associated loss of asthma control or worsening of asthma associated with treatment. No swellings led to airway obstruction or respiratory compromise. No treatment-related anaphylactic shock, life-threatening, or serious treatment-related adverse events were reported for any MK-3641 dose. Of the 1,707 MK-3641-treated subjects, 1 systemic (anaphylactic) reaction was reported (0.06%). The 52-week long-term assessment was generally similar to the safety profile based on the 28-day assessment.

Conclusion: MK-3641 doses up to and including 12 Amb a 1-U were well tolerated, with no unexpected safety findings. Sublingual immunotherapy risks such as worsening asthma or airway swellings that could cause airway obstruction were not observed. Systemic reactions and use of epinephrine were uncommon. In these studies, after the first dose was administered in a health care setting, self-administration was well tolerated.

Trial Registration: clinicaltrials.gov Identifiers: NCT01469182, NCT00783198, NCT00770315, and NCT00978029.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Reprints: Hendrik Nolte, MD, PhD, Merck & Co, Inc, 1 Merck Drive, Whitehouse Station, NJ 08889; E-mail: hendrik.nolte@merck.com.

Disclosure: Dr Nolte is an employee of and owns stock in Merck & Co, Inc. Dr Amar has received research grants from Merck & Co, Inc. Dr Bernstein is a consultant and investigator for Merck & Co, Inc and is director of the American Board of Allergy. Dr Lanier has received research grants from Merck & Co, Inc and Genentech, and is a speaker for Novartis. Dr Creticos has received research grants from and is a speaker for Merck & Co, Inc, Circassia, and Greer, and serves on committees for ACAAI and AAAAI. Dr Berman has received research grants from Merck & Co, Inc. Drs Kaur and Maloney are employees of Merck & Co, Inc. Dr Hébert has nothing to disclose.

Funding: Support for these studies was provided by Merck & Co, Inc, Whitehouse Station, New Jersey.

Introduction

Ragweed pollen is one of the most common inhalant allergens, and for many patients it is a cause of their rhinoconjunctivitis symptoms. One study has shown that 54% of the United States population had at least 1 positive skin test response to 10 common allergens, and 26% were sensitized to ragweed.¹ In Canada, the overall prevalence of a positive allergen skin test was 62.7%, and up to 33% of subjects showed positivity to ragweed.² In addition, ragweed sensitization and clinical allergy are becoming increasingly more prevalent in central Europe because the plant is spreading and pollens are airborne over long distances.^{3,4}

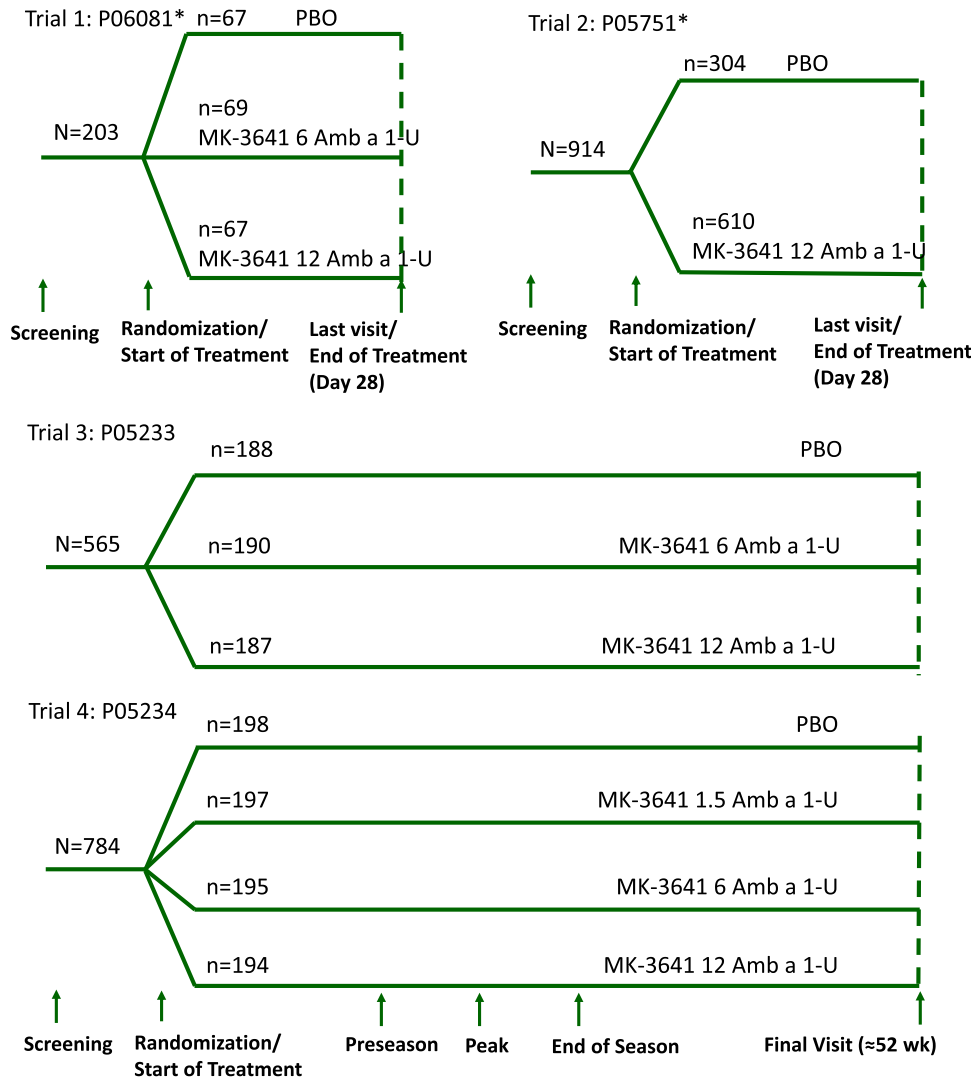


Figure 1. Study design. *P06081 and P05751 were conducted outside the ragweed pollen season. PBO, placebo.

Immunotherapy is the only allergy treatment known to provide long-term benefit and alter the course of respiratory allergic disease.⁵ Allergen immunotherapy has historically been administered by subcutaneous injections, and this remains the most common form of administration in North America.⁶ However, injection therapy requires physician-monitored dose titration to minimize the risk of severe systemic allergic reactions,⁵ and patients may be required to make frequent office visits weekly before a maintenance dose is reached and then for months for 3 to 5 years.⁷ Therefore, new tablet-based immunotherapy formulations that are simple to administer and well tolerated will broaden the treatment options to patients for whom immunotherapy is indicated. Placebo-controlled clinical trials have shown that the 2 modes of administration provide evidence of efficacy; however, sublingual treatment regimens may be associated with a more benign adverse event (AE) profile than injection regimens.^{8,9}

The short ragweed sublingual immunotherapy tablet (SLIT-T) MK-3641 (*Ambrosia artemisiifolia*; Merck Sharp & Dohme Corp, Whitehouse Station, NJ; ALK-Abelló, Hørsholm, Denmark) has been evaluated as a treatment for ragweed pollen-induced allergic rhinitis with or without conjunctivitis (AR/C). An initial phase 1 safety study evaluated a range of doses from 3 to 50 major allergen 1 units (Amb a 1-U) of *A. artemisiifolia* and found that once-daily

MK-3641 at doses up to and including 12 Amb a 1-U were well tolerated up to 28 days in subjects with ragweed-induced AR/C.¹⁰ Subsequently, MK-3641 at doses of 6 and 12 Amb a 1-U were found to be effective and well tolerated in 2 large multinational randomized, placebo-controlled, phase 2 and 3 trials, the primary results of which have been published.^{11,12} MK-3641 also has been studied in 2 unpublished safety trials. The first trial (phase 2) was in adults at least 50 years old and evaluated 2 doses (6 and 12 Amb a 1-U), and a second larger trial (phase 3) was conducted to specifically evaluate the safety of the 12-Amb a 1-U dosage. Given the similarity in the study populations and study designs, all available data from the 4 phase 2 and 3 trials were pooled for post hoc analysis to provide a comprehensive assessment of the overall safety profile of MK-3641 in subjects with ragweed pollen-induced AR/C with or without asthma.

Methods

Trial Designs

Details of key inclusion and exclusion criteria for each of the studies are presented in eTable 1. The protocols for all studies were approved by institutional review boards from each center. All subjects gave written informed consent before any study activity.

Table 1
Demographics and baseline characteristics (all randomized subjects)

Characteristic	28-d Pooled analysis (4 trials)				52-wk Pooled analysis (2 trials)			
	Placebo (n = 757)	MK-3641 1.5 Amb a 1-U (n = 197)	MK-3641 6 Amb a 1-U (n = 454)	MK-3641 12 Amb a 1-U (n = 1,057)	Placebo (n = 386)	MK-3641 1.5 Amb a 1-U (n = 197)	MK-3641 6 Amb a 1-U (n = 385)	MK-3641 12 Amb a 1-U (n = 381)
Age (y), mean (SD)	41 (12)	36 (9)	39 (11)	40 (12)	36 (9)	36 (9)	36 (9)	35 (9)
Women, %	54	56	51	55	49	56	49	52
White, %	78	89	83	83	80	89	83	86
Subjects with asthma, %	18	17	17	18	19	17	18	21
Duration of ragweed allergy (y), mean (SD)	21 (13)	17 (12)	20 (13)	21 (13)	18 (11)	17 (12)	19 (11)	19 (11)
Skin prick test: <i>Ambrosia artemisiifolia</i> average wheal measurement (mm), mean (SD)	10 (4)	11 (4)	11 (4)	9 (4)	11 (4)	11 (4)	11 (4)	11 (4)
Polysensitized (%) ^a	—	—	—	—	81	79	82	82

^aIgE information for polysensitization status was not collected in the 28-day studies.

Trial 1

Trial 1 (P06081, NCT00978029) was a phase 2, multicenter, double-blinded, randomized, parallel-group trial in subjects at least 50 years of age in the United States with ragweed-induced AR/C with or without mild, stable, intermittent asthma conducted from November 2009 to February 2010. Subjects were randomized 1:1:1 by an external randomization group according to a computer-generated randomization schedule to 6 or 12 Amb a 1-U of MK-3641 once daily or matching placebo (Fig 1) without uptitration. Randomization was conducted using an interactive voice response system and was stratified by asthmatic status and age (50–60 and >60 years old). Details of treatment administration and concomitant medication use are listed in eTable 1.

The primary end point was the proportion of subjects experiencing treatment-emergent AEs (TEAEs) during the study. The key secondary end point was the proportion of subjects reporting local AEs expected to occur with sublingual administration of immunotherapy, specifically, oral pruritus, ear pruritus, throat irritation, and mouth edema. An additional secondary end point was the frequency of discontinuations owing to TEAEs. The sample size in the safety studies was based on clinical considerations and no inferential analyses were planned.

Trial 2

Trial 2 (P05751, NCT01469182) was a phase 3, multicenter, double-blinded, randomized, parallel-group trial in subjects at least 18 years of age in the United States and Canada with ragweed-induced AR/C with or without mild, stable asthma conducted from November 2011 to April 2012. Subjects were randomized 2:1 by an external randomization group according to a computer-generated randomization schedule to 12 Amb a 1-U of MK-3641 once daily or matching placebo (Fig 1) without uptitration. Randomization was conducted using an interactive voice response system and was stratified by asthmatic status (yes vs no). Details of treatment administration and concomitant medication use are listed in eTable 1. Of the 4 trials reported, this trial was conducted last. Therefore, owing to the favorable safety profile observed in the previous studies, only the first dose was administered at the study site.

The primary and secondary end points were the same as those described for trial 1. The study was powered to detect rate differences of 3.4% and 11.8%, at placebo incidence rates of 0.5% and 45.0%, respectively, in the primary end point with 90% power at an α level of 0.05.

Trial 3

Trial 3 (P05233, NCT00783198) was a multicenter, double-blinded, randomized, parallel-group, efficacy and safety trial in subjects 18 to 50 years of age in the United States and Canada with ragweed-induced AR/C with or without mild, stable asthma. Details

and results of this trial have been reported.¹¹ Subjects were treated once daily with 6 or 12 Amb a 1-U of MK-3641 or matching placebo (Fig 1) without uptitration. Details of treatment administration and concomitant medication use are listed in eTable 1.

Trial 4

Trial 4 (P05234, NCT00770315) was a multicenter, double-blinded, randomized, parallel-group, efficacy and safety trial in subjects 18 to 50 years of age in North America and Europe with ragweed-induced AR/C with or without mild, stable asthma. Details and results of this trial have been reported.¹² Subjects were treated once daily with 1.5, 6, or 12 Amb a 1-U of MK-3641 or matching placebo (Fig 1) without uptitration. Details of treatment administration and concomitant medication use are listed in eTable 1.

Safety and Tolerability Assessments in All Studies

In all 4 trials, safety and tolerability assessments consisted of AEs, vital signs, physical examinations, and laboratory assessments. AEs were assessed by general questioning at visits. Investigators characterized AEs as mild (awareness of sign or symptom but easily tolerated), moderate (discomfort that interfered with normal activity), severe (incapacitating with inability to perform normal activities or significant effect on clinical status and warranted intervention), or life-threatening (immediate risk of death). Causality was assessed by each investigator as probably related, possibly related, or unlikely related. Treatment-related AEs (TRAEs) included all AEs assessed by the investigator as possibly or probably related to treatment. A serious AE was any AE that met the regulatory definition of seriousness such that the event caused death or was life-threatening, resulted in persistent or significant disability or incapacity, resulted in (or prolonged an existing) inpatient hospitalization, or was a congenital anomaly or birth defect (in an offspring of a subject receiving the study drug). As an added measure to ensure that cases of systemic allergic reactions were not being overlooked, a review of subjects experiencing symptoms affecting 2 organ systems as defined by Food Allergy and Anaphylaxis Network report anaphylaxis criteria was applied to the safety database.¹³

Statistical Analyses in All Studies and Pooled Analyses

Safety analyses were conducted in all randomized subjects who received at least 1 dose of study treatment (all treated). AEs were summarized by treatment group and characterized using descriptive statistics (raw numbers and percentages). AE incidence is reported as the proportion of subjects who developed an AE during the reporting period. Prespecified safety end points of interest were the proportion of subjects experiencing any TEAE, any TEAE leading to study discontinuation, and any prespecified local application-site

Table 2
Adverse event summary (all treated subjects) for each trial

Subjects reporting AE, n (%)	28-d Trials				52-wk Trials			
	Trial 1 (P06081) ^a		Trial 2 (P05751)		Trial 3 (P05233) ^b		Trial 4 (P05234)	
	Placebo (n = 65)	MK-3641 6 Amb a 1-U (n = 66)	MK-3641 12 Amb a 1-U (n = 65)	Placebo (n = 304)	MK-3641 6 Amb a 1-U (n = 188)	MK-3641 12 Amb a 1-U (n = 186)	Placebo (n = 198)	MK-3641 1.5 Amb a 1-U (n = 196)
Any TEAE	29 (44.6)	34 (51.5)	40 (61.5)	130 (42.8)	139 (74.7)	147 (78.2)	125 (63.1)	149 (76.4) ^d
Any TRAE	13 (20.0)	24 (36.4)	27 (41.5)	64 (21.1)	53 (28.5)	112 (59.6)	45 (22.7)	101 (51.8)
Any serious TEAE	0 ^c	0 ^c	1 (1.5) ^c	3 (1.0)	4 (2.2) ^e	2 (1.1) ^e	1 (0.5)	3 (1.5)
Any serious TRAE	0 ^c	0 ^c	0 ^c	1 (0.3)	0 ^c	0 ^c	0	0
Any severe TEAE	1 (1.5)	1 (1.5)	4 (6.2)	9 (3.0)	24 (12.9)	21 (11.2)	25 (12.6)	27 (13.8)
Any severe TRAE	1 (1.5)	1 (1.5)	2 (3.1)	1 (0.3)	1 (0.5)	9 (4.8)	2 (1.0)	6 (3.1)
Any TEAE leading to study discontinuation	1 (1.5) ^c	2 (3.0) ^c	5 (7.7) ^c	3 (1.0)	3 (1.6)	15 (8.0) ^d	6 (3.0)	17 (8.7) ^d
Any TRAE leading to study discontinuation	1 (1.5) ^c	0 ^c	2 (3.0) ^c	2 (0.7)	2 (1.1)	14 (7.4)	4 (2.0)	12 (6.2)
								14 (7.2)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

^aDoes not include information from 7 subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.^bDoes not include information from 5 subjects removed from analysis due to significant departure from Good Clinical Practice by the study site.^cFor all subjects except those removed due to significant departure from Good Clinical Practice.^d $P < .05$ vs placebo by Fisher exact test or Miettinen-Nurminen method. P values were performed only for the prespecified end points of difference in proportion of subjects reporting TEAEs, TEAEs leading to study discontinuation, and local application-site reactions.^eFor all randomized subjects.

reactions (oral pruritus, ear pruritus, throat irritation, and mouth edema). In the individual trials, P values for between-group differences were calculated using the Fisher exact test (trial 1) or the Miettinen-Nurminen method (trials 2, 3, and 4).

Adverse events and the prespecified safety end points defined in the individual studies were assessed in 2 separate pooled analyses. The first analysis used data from the 2 28-day trials and the first 28 days of the 52-week trials (28-day pooled analysis; short-term safety). A second analysis pooled all data (including the first 28 days used in the 28-day pooled analysis) from the 2 52-week studies only (52-week pooled analysis; long-term safety). AEs and the prespecified safety end points are reported descriptively only; no P values for between-group differences of these parameters were calculated for the pooled analyses.

Results

Subjects

In total, 757, 197, 454, and 1,058 subjects were randomized to placebo or 1.5, 6, or 12 Amb a 1-U of MK-3641, respectively. Baseline characteristics for the pooled analyses are presented in Table 1; these characteristics were similar among the individual trials (except the different age groups were based on the inclusion criteria of each study; eTable 2).

Trial 1 (P06081)

In total, 203 subjects were randomized; however, owing to significant departures from Good Clinical Practice, 1 site consisting of 7 subjects was excluded from the safety analysis (these 7 subjects were included in the pooled analysis for completeness). Of the remaining 196 subjects randomized, 186 subjects completed the 28-day study. Eight subjects (4.1%) discontinued owing to AEs (secondary end point; Table 2; $P = .274$ pooled 6 and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TEAEs (primary end point) were 44.6%, 51.5%, and 61.5% in the placebo, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2; $P = .130$ pooled 6 and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TRAEs were 20.0%, 36.4%, and 41.5% in the placebo, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2). As expected, the most common TRAEs were local application-site reactions of oral pruritus and throat irritation (Table 3). There were no notable differences in the proportion of subjects experiencing local application-site reactions (secondary end point) between the 6- and 12-Amb a 1-U MK-3641 groups, although the proportions were significantly larger for the MK-3641 groups vs placebo ($P < .0001$ pooled 6 and 12 Amb a 1-U of MK-3641 vs placebo).

Most subjects (94.1%) who developed TRAEs had AEs assessed as mild to moderate in severity; 4 subjects developed 5 severe TRAEs, and none were life-threatening. No systemic reactions or serious TRAEs occurred, and there were no TRAEs requiring epinephrine use.

Trial 2 (P05751)

Of the 914 subjects randomized, 873 subjects completed the 28-day study and 913 subjects were included in the analysis. Twenty-four subjects (2.6%) discontinued owing to AEs (secondary end point; Table 2; $P = .029$ 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TEAEs (primary end point) were 42.8% and 52.7% in the placebo and 12-Amb a 1-U MK-3641 groups, respectively (Table 2; $P = .005$ 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TRAEs were 21.1% and 39.4% in the placebo and 12-Amb a 1-U MK-3641 groups, respectively (Table 2). The most common TRAEs were local application-site reactions of throat irritation and oral paraesthesia (Table 3). As expected, the proportion of subjects experiencing local application-site reactions (secondary end point) was larger in the 12-Amb a 1-U MK-

Table 3

All treatment-related adverse events occurring in at least 5% of subjects in any treatment group for each trial

Subjects reporting AE, n (%)	28-d Trials				52-wk Trials							
	Trial 1 (P06081) ^a		Trial 2 (P05751)		Trial 3 (P05233) ^b		Trial 4 (P05234)					
	Placebo (n = 65)	MK-3641 6 Amb a 1-U (n = 66)	MK-3641 12 Amb a 1-U (n = 65)	Placebo (n = 304)	MK-3641 12 Amb a 1-U (n = 609)	Placebo (n = 186)	MK-3641 6 Amb a 1-U (n = 188)	MK-3641 12 Amb a 1-U (n = 186)	Placebo (n = 198)	MK-3641 1.5 Amb a 1-U (n = 196)	MK-3641 6 Amb a 1-U (n = 195)	MK-3641 12 Amb a 1-U (n = 194)
Any	13 (20.0)	24 (36.4)	27 (41.5)	64 (21.1)	240 (39.4)	27 (14.5)	99 (52.7)	115 (61.8)	17 (8.6)	55 (28.1)	78 (40.0)	86 (44.3)
Ear pruritus	0	4 (6.1)	5 (7.7)	2 (0.7)	50 (8.2)	4 (2.2)	30 (16.0)	30 (16.1)	2 (1.0)	14 (7.1)	26 (13.3)	24 (12.4)
Eye pruritus	4 (6.2)	2 (3.0)	3 (4.6)	5 (1.6)	7 (1.1)	1 (0.5)	8 (4.3)	8 (4.3)	3 (1.5)	3 (1.5)	3 (1.5)	3 (1.5)
Dry mouth	1 (1.5)	0	4 (6.2)	1 (0.3)	9 (1.5)	2 (1.1)	3 (1.6)	0	1 (0.5)	0	2 (1.0)	2 (1.0)
Oral hypoesthesia	0	1 (1.5)	4 (6.2)	2 (0.7)	10 (1.6)	1 (0.5)	2 (1.1)	2 (1.1)	0	2 (1.0)	6 (3.1)	4 (2.1)
Mouth edema	0	1 (1.5)	0	1 (0.3)	34 (5.6)	0	2 (1.1)	1 (0.5)	0	0	3 (1.5)	2 (1.0)
Oral pruritus	1 (1.5)	11 (16.7)	11 (16.9)	5 (1.6)	43 (7.1)	6 (3.2)	35 (18.6)	36 (19.4)	2 (1.0)	10 (5.1)	28 (14.4)	16 (8.2)
Oral paresthesia	3 (4.6)	3 (4.5)	4 (6.2)	16 (5.3)	70 (11.5)	4 (2.2)	14 (7.4)	20 (10.8)	5 (2.5)	10 (5.1)	15 (7.7)	9 (4.6)
Throat irritation	1 (1.5)	8 (12.1)	5 (7.7)	9 (3.0)	77 (12.6)	10 (5.4)	48 (25.5)	54 (29.0)	7 (3.5)	24 (12.2)	41 (21.0)	41 (21.1)
Swollen tongue	1 (1.5)	3 (4.5)	3 (4.6)	0	4 (0.7)	6 (3.2)	22 (11.7)	36 (19.4)	1 (0.5)	11 (5.6)	11 (5.6)	13 (6.7)
Pruritus	2 (3.1)	1 (1.5)	1 (1.5)	6 (2.0)	13 (2.1)	0	12 (6.4)	9 (4.8)	4 (2.0)	3 (1.5)	7 (3.6)	4 (2.1)

Abbreviation: AE, adverse event.

^aDoes not include information from 7 subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.^bDoes not include information from 5 subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.

3641 group compared with placebo. The proportion of subjects who developed oral pruritus, ear pruritus, throat irritation, and mouth edema was significantly larger in the 12-Amb a 1-U MK-3641 group compared with placebo ($P < .001$ for all comparisons).

Most subjects (96.4%) who developed TRAEs had AEs assessed as mild to moderate in severity; 10 subjects in the 12-Amb a 1-U MK-3641 group developed 10 severe TRAEs, and 1 subject in the placebo group developed a severe TRAE. None of the events in the 12-Amb a 1-U MK-3641 group were considered life-threatening. No serious TRAEs were experienced by subjects in the 12-Amb a 1-U MK-3641 group. Four subjects (3 receiving 12 Amb a 1-U of MK-3641 and 1 receiving placebo) received epinephrine. One 22-year-old woman randomized to 12 Amb a 1-U of MK-3641 developed local application events starting on day 3 of treatment. Owing to worsening of the events, the next dose of study drug was administered under supervision in the investigator's office. Within 5 minutes of taking 12 Amb a 1-U of MK-3641, the subject developed mouth swelling and dysphagia. The subject was treated with epinephrine, albuterol, and an antihistamine. The investigator considered the AE to be moderate in severity and probably related to study medication. The subject fully recovered and discontinued from the trial. A 34-year-old man who was randomized to 12 Amb a 1-U of MK-3641 developed local application-site reactions starting at day 1. On day 6, he developed ear and throat pruritus within 5 minutes of dosing; within 30 minutes, the subject developed nausea, increased salivation, a lump in the throat, a swollen lower lip, faintness, mild blurred vision, a swollen throat, and mild shortness of breath. This event was considered a nonserious anaphylactic reaction. The subject self-administered epinephrine and proceeded to an emergency department for further evaluation and treatment. Examination in the emergency department found no objective swelling or wheeze and a normal physical examination result, and the subject was discharged without hospital admission. The investigator considered the event severe and probably related to treatment. The subject fully recovered after treatment and discontinued from the trial. A 41-year-old man who was randomized to 12 Amb a 1-U of MK-3641 self-administered epinephrine in response to throat tightness assessed as severe in intensity on day 14 of treatment, approximately 2 hours after the onset of the event. The investigator assessed the event as a severe local reaction probably related to study drug but did not assess epinephrine as necessary for treatment. A 45-year-old woman with a history of latex allergy who was randomized to placebo developed urticaria within 5 minutes of the first dosing. The subject was treated with an antihistamine. Within 1 hour the subject developed cough, dyspnea, pharyngeal pruritus, and thoracic pain, which were assessed as an anaphylactic reaction. Epinephrine was given by the physician and was administered again en route to the emergency facility. The event was reported as an anaphylactic reaction and assessed as life-threatening.

Trial 3 (P05233)

Results from this trial have been described previously.¹¹ Of the 565 subjects randomized, 423 subjects completed the study and 560 subjects were included in the safety analysis. Thirty-seven subjects (6.5%) discontinued owing to AEs (Table 2; $P = .001$ pooled 6 and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TEAEs were 74.7%, 78.2%, and 84.9% in the placebo, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2; $P = .061$ pooled 6 and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TRAEs were 28.5%, 59.6%, and 68.8% in the placebo, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2). The most common TRAEs were local application-site reactions of throat irritation and oral pruritus (Table 3). There were no notable differences in the proportion of subjects experiencing local application-site reactions

Table 4

Adverse event summary (all treated subjects) for pooled analyses

Subjects reporting AE, n (%)	28-d Pooled analysis (4 trials)				52-wk Pooled analysis (2 trials)			
	Placebo (n = 757)	MK-3641 1.5 Amb a 1-U (n = 196)	MK-3641 6 Amb a 1-U (n = 454)	MK-3641 12 Amb a 1-U (n = 1,057)	Placebo (n = 386)	MK-3641 1.5 Amb a 1-U (n = 196)	MK-3641 6 Amb a 1-U (n = 385)	MK-3641 12 Amb a 1-U (n = 381)
Any TEAE	285 (37.6)	97 (49.5)	261 (57.5)	597 (56.5)	264 (68.4)	148 (75.5)	296 (76.9)	307 (80.6)
Any TRAE	155 (20.5)	70 (35.7)	230 (50.7)	482 (45.6)	98 (25.4)	79 (40.3)	213 (55.3)	233 (61.2)
Any serious TEAE	4 (0.5)	0	1 (0.2)	2 (0.2)	4 (1.0)	4 (2.0)	5 (1.3)	3 (0.8)
Any serious TRAE	1 (0.1)	0	0 (0)	0 (0)	0	0	0	0
Any severe TEAE	21 (2.8)	1 (0.5)	18 (4.0)	43 (4.1)	49 (12.7)	26 (13.3)	48 (12.5)	63 (16.5)
Any severe TRAE	3 (0.4)	0	10 (2.2)	22 (2.1)	3 (0.8)	1 (0.5)	15 (3.9)	16 (4.2)
Any TEAE leading to study discontinuation	7 (0.9)	4 (2.0)	24 (5.3)	55 (5.2)	9 (2.3)	10 (5.1)	31 (8.1)	35 (9.2)
Any TRAE leading to study discontinuation	6 (0.8)	3 (1.5)	19 (4.2)	46 (4.4)	6 (1.6)	4 (2.0)	26 (6.8)	31 (8.1)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

between the 6- and 12-Amb a 1-U MK-3641 groups. The proportion of subjects who developed oral pruritus, ear pruritus, and throat irritation was significantly larger in the 6- and 12-Amb a 1-U MK-3641 groups compared with placebo ($P < .001$ for all comparisons).

Most subjects (92.8%) who developed TRAEs had AEs assessed as mild or moderate in severity; 21 subjects developed severe TRAEs, and none were life-threatening. No systemic reactions or serious TRAEs occurred. One subject in the 6-Amb a 1-U MK-3641 group was treated with epinephrine, diphenhydramine, and methylprednisolone in the emergency department for the sensation of localized pharyngeal edema (no objective swelling was observed at physical examination) that developed within 1 minute of dosing on day 22 of treatment. The event was considered likely related to study treatment and the subject discontinued the study.

Trial 4 (P05234)

Results from this trial have been described previously.¹² Of the 784 subjects randomized, 606 subjects completed the study and 783 subjects were included in the safety analysis. Fifty subjects (6.4%) discontinued owing to AEs (Table 2; $P = .036$ pooled 1.5, 6, and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TEAEs were 63.1%, 75.5%, 76.4%, and 76.8% in the placebo, 1.5-, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2; $P < .001$ pooled 1.5, 6, and 12 Amb a 1-U of MK-3641 vs placebo). The proportions of subjects experiencing TRAEs were 22.7%, 40.3%, 51.8%, and 54.1% in the placebo, 1.5-, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 2). The most common TRAEs were local application-site reactions of throat irritation and oral pruritus (Table 3). There were no notable differences in the proportion of subjects experiencing local application-site reactions between the 6- and 12-Amb a 1-U MK-3641 groups. The proportion of subjects who developed oral pruritus, ear pruritus, and throat irritation was significantly larger in the 1.5-, 6-, and 12-Amb a 1-U MK-3641 groups compared with placebo ($P \leq .011$ for all comparisons).

Table 5

All treatment-related adverse events occurring in at least 5% of subjects in any treatment group in the pooled analyses

Subjects reporting AE, n (%)	28-d Pool (4 trials)				52-wk Pool (2 trials)			
	Placebo (n = 757)	MK-3641 1.5 Amb a 1-U (n = 196)	MK-3641 6 Amb a 1-U (n = 454)	MK-3641 12 Amb a 1-U (n = 1,057)	Placebo (n = 386)	MK-3641 1.5 Amb a 1-U (n = 196)	MK-3641 6 Amb a 1-U (n = 385)	MK-3641 12 Amb a 1-U (n = 381)
Any	155 (20.5)	70 (35.7)	230 (50.7)	482 (45.6)	98 (25.4)	79 (40.3)	213 (55.3)	233 (61.2)
Ear pruritus	8 (1.1)	14 (7.1)	59 (13.0)	110 (10.4)	6 (1.6)	14 (7.1)	53 (13.8)	53 (13.9)
Mouth edema	4 (0.5)	7 (3.6)	32 (7.0)	64 (6.1)	12 (0.5)	9 (4.6)	37 (9.6)	35 (9.2)
Oral pruritus	15 (2.0)	10 (5.1)	87 (19.2)	115 (10.9)	10 (2.6)	11 (5.6)	81 (21.0)	66 (17.3)
Oral paresthesia	30 (4.0)	12 (6.1)	35 (7.7)	106 (10.0)	11 (2.8)	12 (6.1)	31 (8.1)	32 (8.4)
Swollen tongue	4 (0.5)	7 (3.6)	13 (2.9)	31 (2.9)	4 (1.0)	8 (4.1)	12 (3.1)	32 (8.4)
Tongue pruritus	4 (0.5)	9 (4.6)	27 (5.9)	54 (5.1)	4 (0.8)	9 (4.6)	27 (7.0)	24 (6.3)
Throat irritation	25 (3.3)	23 (11.7)	94 (20.7)	175 (16.6)	17 (4.4)	23 (11.7)	89 (23.1)	95 (24.9)

Abbreviation: AE, adverse event.

Most subjects (95.8%) who developed TRAEs had AEs assessed as mild to moderate in severity; 14 subjects developed severe TRAEs, and none were life-threatening. No systemic reactions or serious TRAEs occurred, and there were no TRAEs requiring epinephrine use.

28-Day Pooled Analysis (Short-Term Safety)

In total, 2,464 subjects from all 4 MK-3641 phase 2 and 3 studies were assessed in the 28-day pooled analysis to provide a more comprehensive assessment of safety. Ninety subjects (3.7%) discontinued owing to AEs (Table 4). The proportions of subjects experiencing TEAEs were 37.6%, 49.5%, 57.5%, and 56.5% in the placebo, 1.5-, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 4). The proportions of subjects experiencing TRAEs were 20.5%, 35.7%, 50.7%, and 45.6% in the placebo, 1.5-, 6-, and 12-Amb a 1-U MK-3641 groups, respectively (Table 4). As was observed in the individual trials, the most common TRAEs were local application-site reactions (Table 5). The most prevalent TRAEs were throat irritation and oral pruritus.

Most subjects (96.3%) who developed TRAEs had AEs assessed as mild to moderate in severity (eFig 1). The occurrence of severe TRAEs was similar in the 6- and 12-Amb a 1-U MK-3641 groups, which was slightly higher than in the 1.5-Amb a 1-U MK-3641 and placebo groups (Table 4). In the 6-Amb a 1-U MK-3641 group, no severe TRAEs were experienced by more than 1 subject. In the 12-Amb a 1-U MK-3641 group, the only severe TRAEs experienced by more than 1 subject were mouth edema ($n = 4$) and swollen tongue, oral pruritus, dysphagia, oropharyngeal pain, and throat tightness (each $n = 2$). Severe local swellings can lead to airway compromise. However, no swellings led to airway obstruction or respiratory compromise. There were no life-threatening or serious TRAEs in any of the MK-3641 groups. Of the 1,707 subjects treated with MK-3641, 1 nonserious anaphylactic reaction (reported in P05751) occurred, resulting in a systemic reaction (including anaphylactic reaction) incidence rate of 0.06%.

Onset of treatment-related local application-site reactions was generally within the first few days of treatment initiation. For the 6-

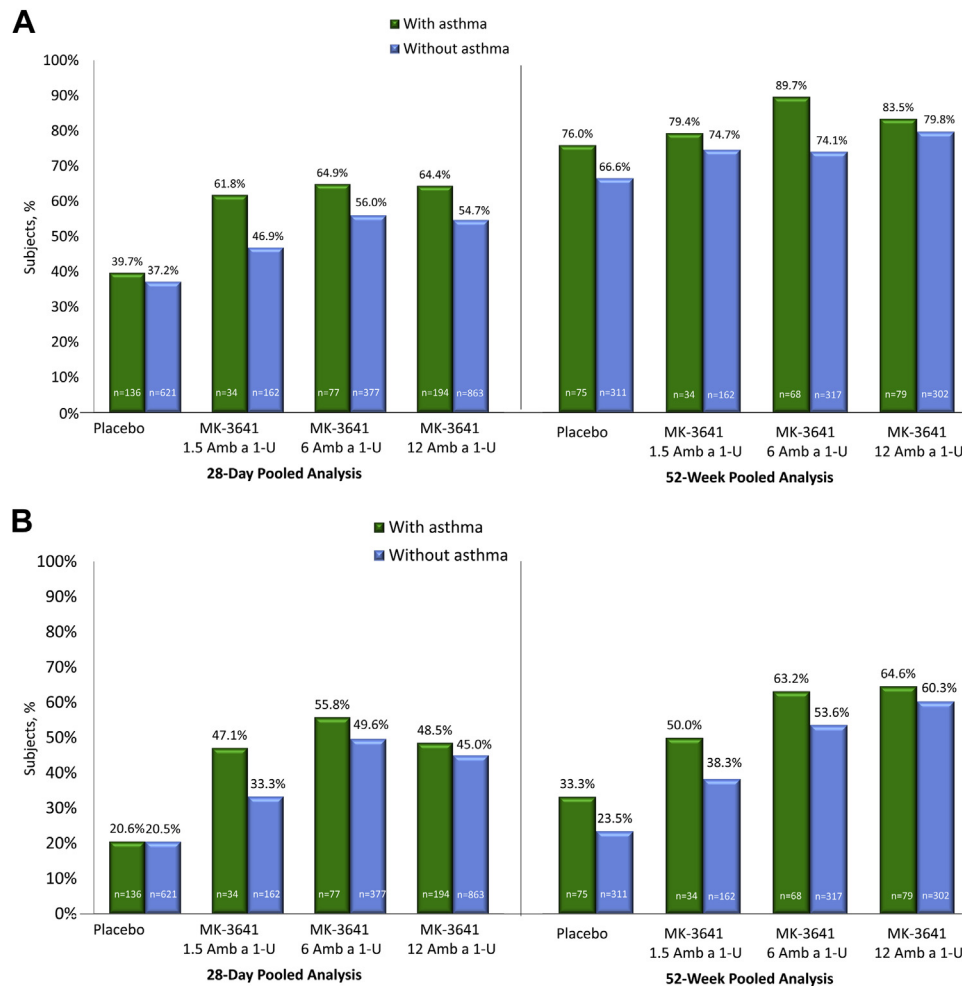


Figure 2. Percentages of subjects with and without asthma developing (A) treatment-emergent adverse events and (B) treatment-related adverse events in the 28-day pooled analysis (4 trials) and 52-week pooled analysis (2 trials).

and 12-Amb a 1-U MK-3641 doses, the median time to onset of ear pruritus, glossodynia, oral hypoesthesia, oral discomfort, oral pruritus, oral paresthesia, throat irritation, oropharyngeal swelling, lip swelling, and stomatitis was 1 to 4 days. No dose response in relation to onset of local application site-reactions was evident. For subjects in the 6- and 12-Amb a 1-U MK-3641 groups, individual local application-site reactions reoccurred after tablet administration for a median no longer than 9 days. Local reactions were transient as reported anecdotally by investigators (no evaluation of duration in minutes was conducted).

52-Week Pooled Analysis (Long-Term Safety)

The overall AE profile from the 52-week pooled analysis (2 trials) was generally similar to the 28-day pooled analysis (which included the first 28 days of the 52-week trials), providing evidence of long-term safety (Tables 4 and 5). For subjects in the MK-3641 treatment groups who developed TRAEs, most events (95%) were within the first 28 days of treatment.

Adverse Events in Subjects With and Without Asthma

In the 28-day and 52-week pooled analysis, TEAE and TRAE rates were slightly higher in the subpopulation of subjects with asthma compared with those without asthma (Fig 2); however, the characteristics and severity of AEs were similar when comparing the subpopulation of subjects with and without asthma. In subjects with and without asthma, the most common TRAEs in the 28-day

pooled analysis for the 6- and 12-Amb a 1-U doses were throat irritation, ear pruritus, and oral pruritus.

Other Safety Assessments

No clinically relevant changes in vital signs, pulmonary function tests, or laboratory values were observed in any of the 4 studies.

Discussion

In contrast to previous immunotherapy studies, these 4 studies undertook a rigorous approach to safety evaluation, using prospective methods of AE collection and with predefined safety end points in the 28-day trials. In addition, the pooled analyses were undertaken to provide a comprehensive assessment of ragweed SLIT-T short-term and long-term safety. Pooling of the data into 1 large population (2,464 subjects in the 28-day pool) allowed for evaluation among treatment groups compared with reviewing results from each trial independently. Results from the individual trials and the pooled analyses indicate that ragweed SLIT-T is generally well tolerated. TRAEs were higher with the 6- and 12-Amb a 1-U doses compared with placebo and consisted of primarily transient mild-to-moderate local application-site events. The AE profiles of the 6- and 12-Amb a 1-U doses were similar, whereas the frequency and intensity of AEs were lower for the 1.5-Amb a 1-U dose. The AE profile observed in the 52-week pooled analysis was largely comparable to that observed in the 28-day pooled analysis, supporting the fact that the AE profile over the

first 28 days of SLIT administration (short-term safety) can be considered generally representative of long-term tolerability.

In 3 of the studies, tablet administration was directly observed for the first 3 days to intervene in the event of a severe immediate allergic reaction to initial doses; in P05751 (the final large 28-day trial confirming tolerability of the 12-Amb a 1-U dose), only the first dose was given at the study site based on the reassuring data over the first 3 days in prior trials. No additional safety concerns became evident when only the first dose was supervised. Furthermore, no serious TRAEs occurred after day 1 (or at any time) in any of the studies, suggesting that a single day of on-site dosing is sufficient. A 30-minute observation period after the on-site dosing is supported by the fact that no delayed systemic reactions in relation to the daily tablet administration occurred in any of the studies. Although no treatment-related serious systemic reactions occurred, 1 subject developed a nonserious anaphylactic reaction. This reaction was readily detected by the subject who self-medicated with epinephrine and proceeded to the emergency department, where the event was managed with standard pharmacotherapy.

The World Allergy Organization and Allergic Rhinitis and its Impact on Asthma considers SLIT to be sufficiently well tolerated and that at-home administration is acceptable.^{6,14} The safety profile of these trials reaffirm this assessment. In these 4 clinical trials, 4 events related to MK-3641 use were treated with epinephrine, and approximately 2% of subjects in the 6- and 12-Amb a 1-U MK-3641 groups developed severe TRAEs in the 28-day pooled analysis. It is unknown if the incidence of epinephrine use and severe AEs will be comparable in clinical practice. The definitions and criteria used for safety assessment in clinical trials are more rigorous than those used in everyday clinical practice. Furthermore, investigators in clinical trials tend to be more conservative when assessing safety and may be more likely to administer or encourage epinephrine use in a manner that differs from real-world clinical practice. It is still a matter for debate as to whether epinephrine should be prescribed for patients receiving SLIT because, as shown by 1 subject in this analysis, unwarranted use will occur. Of the uses of epinephrine in response to TRAEs in subjects receiving MK-3641, none were rapidly progressing; symptoms progressed at a rate permitting subjects to appropriately self-treat or proceed to an appropriate care facility.

Immunotherapy has been used with caution in patients with asthma because of an increased risk of serious systemic reactions and severe AEs.^{15,16} The pooled analyses of MK-3641 indicated the characteristics and severity of AEs were similar when comparing the subpopulation of subjects with and without mild, stable asthma receiving the 6- and 12-Amb a 1-U MK-3641 doses. The safety of ragweed SLIT-T in patients with asthma and a forced expiratory volume in 1 second lower than 70% who require asthma medications other than low-dose inhaled corticosteroids is currently unknown. In addition, there is limited immunotherapy safety data in patients at least 50 years old and it appears from the ragweed safety trial in older patients that MK-3641 was well tolerated in this age group.

Four published placebo-controlled, randomized trials have assessed the safety of ragweed SLIT; all 4 trials used drop formulations.^{17–20} The total duration of full-dose treatment in all of these trials was shorter than 28 weeks, and 2 of the trials used up-treatment schedules. Thus, differences in product formulation (tablet vs drop) and titration schedules make it difficult to make a safety comparison of these studies.

In conclusion, results from the individual trials and the pooled safety analyses indicate that MK-3641 is well tolerated during up to 1 year of treatment. In contrast to grass SLIT-T, in which there is real-world experience from Europe indicating that SLIT is safe and well tolerated, there is limited safety experience with ragweed SLIT-T. However, in the subjects who participated in these trials,

after the first dose was taken under medical supervision, self-administration was shown to be well tolerated.

Acknowledgments

Medical writing and editorial assistance was provided by Rob Coover, MPH, and Erin P. Scott, PhD, of Adelphi Communications (New York, New York). This assistance was funded by Merck & Co, Inc, Whitehouse Station, New Jersey. Editorial assistance also was provided by Jorge Moreno-Cantu, PhD, Global Scientific and Medical Publications, Office of the Chief Medical Officer, Merck & Co. Additional statistical assistance was provided by Nancy Liu, PhD, formerly of Merck & Co., Inc (Whitehouse Station, New Jersey).

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.04.018>.

References

- Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116:377–383.
- Chan-Yeung M, Anthonisen NR, Becklake MR, et al. Geographical variations in the prevalence of atopic sensitization in six study sites across Canada. *Allergy*. 2010;65:1404–1413.
- Burbach GJ, Heinzerling LM, Rohnelt C, et al. Ragweed sensitization in Europe—GA²LEN study suggests increasing prevalence. *Allergy*. 2009;64:664–665.
- Gaudeul M, Giraud T, Kiss L, Shykoff JA. Nuclear and chloroplast microsatellites show multiple introductions in the worldwide invasion history of common ragweed, *Ambrosia artemisiifolia*. *PLoS One*. 2011;6:e17658.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(suppl):S1–S55.
- Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy*. 2009;64:1–59.
- Jourdy DN, Reisacher WR. Factors affecting time required to reach maintenance dose during subcutaneous immunotherapy. *Int Forum Allergy Rhinol*. 2012;2:294–299.
- Moingeon P, Mascarell L. Induction of tolerance via the sublingual route: mechanisms and applications. *Clin Dev Immunol*. 2012;2012:623474.
- Dretzke J, Meadows A, Novielli N, et al. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol*. 2013;131:1361–1366.
- Nayak AS, Atiee GJ, Dige E, Maloney J, Nolte H. Safety of ragweed sublingual allergy immunotherapy tablets in adults with allergic rhinoconjunctivitis. *Allergy Asthma Proc*. 2012;33:404–410.
- Nolte H, Hébert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol*. 2013;110:450–456.e4.
- Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol*. 2013;131:1342–1349.e6.
- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and AllerGen). *Allergy*. 2008;63:8–160.
- Iglesias-Cadarsa A, Hernandez-Weigand P. Risk factors for systemic reactions to allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2011;11:579–585.
- Passalacqua G, Canonica GW. Specific immunotherapy in asthma: efficacy and safety. *Clin Exp Allergy*. 2011;41:1247–1255.
- André C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol*. 2003;131:111–118.
- Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2004;93:425–430.
- Skoner D, Gentile D, Bush R, et al. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol*. 2010;125:660–666.
- Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2014;133:751–758.

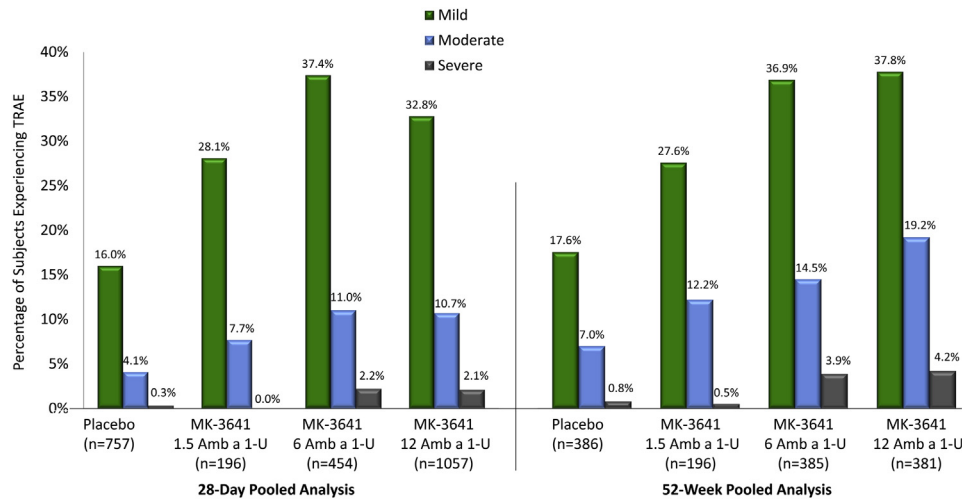


Figure 1. Percentages of subjects developing treatment-related adverse events (TRAEs) by severity in the 28-day pooled analysis (4 trials) and 52-week pooled analysis (2 trials).

eTable 1
Key trial design details

	Inclusion criteria	Exclusion criteria	Treatment administration	Concomitant medication
28-d studies				
Trial 1 (P06081)	either sex	history of severe asthma	28 d of treatment outside RS	washout period before randomization: 7 d for antihistamines and decongestants, ≥ 30 d for corticosteroids
	any race	asthma requiring any inhaled corticosteroids	first 3 doses administered at study site followed by 30-min observation period	allergy rescue medication not allowed
	≥ 50 y old	requirement for antiallergery medications after washout period	subsequent doses administered without medical supervision	subjects supplied with self-injectable epinephrine in event of acute severe systemic reaction
	clinical history of ragweed-induced AR/C of ≥ 2 y duration, with or without asthma positive skin prick test response (≥ 5 -mm wheal compared vs saline control) FEV ₁ $\geq 70\%$ of predicted value	history of anaphylaxis with cardiorespiratory symptoms, chronic urticaria, and angioedema		
Trial 2 (P05751)	either sex	unstable asthma or history of asthma deterioration resulting in emergency treatment, hospitalization, or treatment with systemic corticosteroids within 3 mo before screening	28 d of treatment outside RS	washout period before randomization: 7 d for antihistamines and decongestants, ≥ 30 d for corticosteroids
	any race	requirement for antiallergery medications after washout period	first dose administered only at study site followed by 30-min observation period	allergy rescue medication not allowed
	≥ 18 y old	history of anaphylaxis with cardiorespiratory symptoms, chronic urticaria, and angioedema	subsequent doses administered without medical supervision	subjects supplied with self-injectable epinephrine in event of acute severe systemic reaction
	clinical history of ragweed-induced AR/C of ≥ 2 y duration, with or without asthma positive skin prick test response (≥ 5 -mm wheal vs saline control) FEV ₁ $\geq 70\%$ of predicted value			
52-wk studies				
Trials 3 (P05233) and 4 (P05234)	either sex	history of symptomatic seasonal AR and/or asthma to another allergen potentially overlapping ragweed pollen season	treatment initiated 16 wk before RS, continued during RS and after season for total treatment period of approximately 52 wk	washout period before randomization: 7 d for antihistamines and decongestants, ≥ 30 d for corticosteroids
	any race	history of symptomatic perennial AR to an allergen to which subject is regularly exposed	first 3 doses administered at study site followed by 30-min observation period	low-dose inhaled corticosteroids for asthma allowed
	18–50 y old	history of severe asthma	subsequent doses administered without medical supervision	during RS only, subjects provided open-label allergy rescue medication to use in stepwise manner if prespecified AR/C symptom thresholds were met
	clinical history of ragweed-induced AR/C of ≥ 2 y duration, with or without asthma positive skin prick test response (≥ 5 -mm wheal vs saline control) specific IgE (class 2; ≥ 0.7 kU/L) to <i>Ambrosia artemisiifolia</i> at screening FEV ₁ $\geq 70\%$ of predicted value	asthma requiring medium- or high-dose inhaled corticosteroids history of anaphylaxis with cardiorespiratory symptoms, chronic urticaria, and angioedema history of chronic sinusitis within past 2 y		subjects supplied with self-injectable epinephrine in event of acute severe systemic reaction

Abbreviations: AR, allergic rhinitis; AR/C, allergic rhinitis with or without conjunctivitis; FEV₁, forced expiratory volume in 1 second; RS, ragweed pollen season.

eTable 2

Demographics and baseline characteristics for each trial

Characteristic	Trial 1 (P06081) ^a			Trial 2 (P05751)			Trial 3 (P05233) ^b			Trial 4 (P05234)			
	Placebo (n = 65)	MK-3641 6 Amb a 1-U (n = 66)	MK-3641 12 Amb a 1-U (n = 65)	Placebo (n = 304)	MK-3641 12 Amb a 1-U (n = 610)		Placebo (n = 186)	MK-3641 6 Amb a 1-U (n = 188)	MK-3641 12 Amb a 1-U (n = 186)	Placebo (n = 198)	MK-3641 1.5 Amb a 1-U (n = 197)	MK-3641 6 Amb a 1-U (n = 195)	MK-3641 12 Amb a 1-U (n = 194)
Age (y), mean (SD)	56 (5)	56 (5)	56 (6)	42 (12)	41 (13)		36 (9)	35 (9)	35 (9)	37 (9)	36 (9)	37 (9)	36 (9)
Women, %	58	65	62	58	57		50	44	58	49	56	53	47
White, %	83	85	85	75	81		74	80	82	85	89	87	89
Subjects with asthma, %	11	14	9	18	18		23	20	23	16	17	16	19
Skin prick test: <i>Ambrosia artemisiifolia</i> average wheal measurement (mm), mean (SD)	9 (3)	8 (3)	9 (4)	9 (4)	9 (4)		11 (4)	12 (4)	11 (4)	12 (4)	12 (4)	13 (5)	12 (4)
Polysensitized (%) ^c	—	—	—	—	—		85	86	85	76	79	78	79

^aDoes not include information from 7 subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.^bDoes not include information from 5 subjects removed from analysis owing to significant departure from Good Clinical Practice by the study site.^cIgE information for polysensitization status was not collected in the 28-day studies.