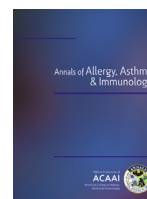




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Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial

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ABSTRACT

Background: In North America, few studies have evaluated sublingual immunotherapy for allergic rhinitis with or without conjunctivitis (AR/C); pediatric data are sparse. The authors report findings from the largest published immunotherapy trial yet conducted in adults and children.

Objective: To evaluate grass sublingual immunotherapy tablet (MK-7243) treatment in subjects with AR/C. **Methods:** North American subjects (5–65 years old) with grass allergy were randomized 1:1 to once-daily MK-7243 (2,800 BAU *Phleum pratense*) or placebo. The first dose was given at the investigator's office; subsequent doses were self-administered at home. The primary end point was total combined score (TCS; rhinoconjunctivitis daily symptom score [DSS] plus daily medication score [DMS]) over the entire grass pollen season (GPS). Key secondary end points included entire-season DSS, DMS, peak-season TCS, and rhinoconjunctivitis quality-of-life questionnaire scores. Safety outcomes included adverse events (AEs).

Results: One thousand five hundred one subjects were randomized (85% polysensitized, 25% had asthma). MK-7243 yielded improvements vs placebo of 23% in entire-season TCS (median difference −0.98, $P < .001$), 29% in peak-season TCS (median difference −1.33, $P < .001$), 20% in entire-season DSS (median difference −0.64, $P = .001$), 35% in entire-season DMS (mean difference −0.48, $P < .001$), and 12% in peak-season rhinoconjunctivitis quality-of-life questionnaire (median difference −0.13, $P = .027$). Efficacy between children and adults was similar. Most AEs were transient local application-site reactions, with no serious treatment-related AEs or anaphylactic shock. Three subjects (1 placebo, 2 MK-7243) had moderate systemic allergic reactions.

Conclusion: MK-7243 was effective in polysensitized grass-allergic North American children and adults with AR/C in this large trial, confirming previous research.

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Introduction

Allergic rhinitis with or without conjunctivitis (AR/C) is a prevalent atopic condition that is estimated to occur in 18% of Americans at least 5 years old according to a recent national survey.¹ Many patients with AR/C experience symptoms upon exposure to grass pollen; in some regions of the United States, an estimated 50% to 70% of patients with AR/C are sensitized to grass allergens.^{2–4} Timothy grass (*Phleum pratense*), a member of the Pooideae subfamily, has been shown to be highly cross-reactive with other Pooideae members, including cocksfoot (also known as orchard grass), Kentucky bluegrass (also known as June grass), perennial rye, sweet vernal, reedtop, and meadow fescue, and is partly cross-reactive with Johnson grass; these species are all major aeroallergens in North America.^{5,6}

Many patients with AR/C rely on long-term symptomatic pharmacotherapy; immunotherapy offers potential for a disease-modifying effect and an associated decreased reliance on symptomatic medication.⁷ Allergy immunotherapy historically has been administered subcutaneously, and this remains the typical form of administration in North America.⁸ However, injection therapy requires physician monitoring to recognize and treat systemic allergic reactions,⁷ and weekly visits may be necessary for months before a maintenance dose is reached.⁹ An administration method permitting a single day's in-office administration with no up-titration schedule offers a major improvement in convenience.

Clinical trial evidence suggests that sublingual tablet treatments may be associated with a relatively benign adverse event (AE) profile, primarily including expected mild to moderate local reactions.^{10–16} This may translate into a safety advantage in clinical practice; after the first dose has been administered and observed to be tolerated under medical supervision, patients may then be permitted to self-treat at home. The timothy grass sublingual allergy immunotherapy tablet, MK-7243 (2,800 BAU *P pratense*; Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey; and ALK-Abelló, Hørsholm, Denmark), has been found effective and well tolerated for AR/C induced by timothy and related grasses in European and North American pediatric and adult clinical trials.^{10–13} MK-7243 was administered at investigational sites for the first 3 daily doses in previous North American trials. Standard practice in Europe is to administer only the first dose under medical supervision, and this study evaluated this approach in a North American population. Furthermore, this study adds to the accumulated efficacy and safety data for this therapy, with the largest double-blinded, randomized, controlled trial of immunotherapy yet described in adults and children. This trial evaluated treatment with MK-7243 in North American subjects with grass-pollen-induced AR/C.

Methods

Study Design

This was a multicenter, double-blinded, randomized, placebo-controlled, parallel-group study (P08067; clinicaltrials.gov; registration NCT01385371) conducted in the United States and 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; all subjects gave written informed consent before any study activity commenced.

After informed consent was obtained, subjects were screened. A total of 1,501 subjects who continued to qualify for the study were randomized in a 1:1 ratio according to a computer-generated randomization schedule; randomization was conducted by an external randomization group using an interactive voice response system and was stratified by asthmatic status and age category

(≥ 5 – <18 or ≥ 18 – ≤ 65 years). The sponsor created 1 set of randomization schedules for subject randomization numbers and another for kit numbers. Subjects were to receive placebo or MK-7243 with no up-titration, initiated at a daily maintenance dose of 2,800 BAU (75,000 Standardized Quality Units tablet; approximately 15 μ g of Phl p 5). The dose selection was based on previous studies in which 2,800 BAU of MK-7243 was found to be well tolerated and effective in children and adults.^{10–13} The tablets were supplied as fast-dissolving (within seconds on the mucosa), neutral-tasting oral lyophilisates for sublingual administration. The study drug and matching placebo were packaged in identical blister cards packaged in kits identified with kit numbers. The sponsor, subject, and investigational staff (investigator and evaluators) were blinded to treatment. Placebo was indistinguishable from the active tablet in appearance, smell, and taste but contained no pollen extract. Subjects were treated once daily with placebo or MK-7243 for at least 12 weeks before and during the entire 2012 grass pollen season (GPS; eFig 1).

A washout period (≥ 30 days) for inhaled corticosteroids before the preseasonal visit (approximately 2 weeks before the start of GPS) was required. During the GPS, all subjects had access to pre-defined, open-label allergy rescue medications to use in a stepwise manner beginning if a prespecified daily symptom score (DSS) threshold was met (eFig 2). The first dose of MK-7243 or placebo was administered at the study site, with subjects monitored for 30 minutes after dosing for AEs. Subsequent doses were self-administered at home at approximately the same time daily (for children, dosing was to be conducted at a time permitting the parent/guardian to keep the subject under observation for AEs for approximately 30 minutes after administration). As a precaution, each subject was supplied with self-injectable epinephrine to be used in the event of an acute, severe, local, or systemic allergic reaction. Investigators educated subjects about expected local application-site reactions and informed subjects that epinephrine was not intended for such reactions.

Study Subjects

Eligible subjects were 5 to 65 years old, of either sex and any race, with a physician-diagnosed history of grass pollen-induced AR/C with or without asthma who had received treatment for their AR/C during the previous GPS. At screening, subjects were required to meet the following criteria: positive skin prick test response to *P pratense* (≥ 5 -mm wheal compared with saline control, 100,000 BAU/mL; ALK-Abelló, Round Rock, Texas); positive specific IgE against *P pratense* ($\geq$ IgE class 2; ≥ 0.7 kU/L); and a forced expiratory volume in 1 second at least 70% of the predicted value at screening and randomization visits.

Key reasons for exclusion included a clinical history of symptomatic AR/C and/or asthma requiring regular medications for another seasonal allergen during or potentially overlapping with the GPS or for a perennial allergen to which the subject was regularly exposed; immunosuppressive treatment within the past 3 months (except steroids for allergic/asthma symptoms); a history of severe asthma; and previous immunotherapy with any grass pollen allergen for longer than 1 month within the last 5 years. Additional inclusion and exclusion criteria are listed in the eMethods section.

Grass Pollen Season

The 2012 GPS, determined for each site, was defined as beginning on the first of 3 consecutive days with a grass pollen count ≥ 10 grains/m³ and ending on the last day of the last occurrence of 3 consecutive days with a grass pollen count ≥ 10 grains/m³. Peak season was defined as the 15 consecutive days within the GPS with the highest 15-day moving average pollen count for each site.

Clinical Efficacy Assessments

The primary end point was the total combined score (TCS), the sum of the DSS and daily medication scores (DMS), averaged over the GPS. Key secondary end points were the average DSS over the GPS, the average TCS during the peak GPS, the average rhinoconjunctivitis quality-of-life questionnaire with standardized activities for subjects ≥ 12 years of age (RQLQ[S]12+) score during the peak GPS, and the average DMS over the GPS. Additional secondary efficacy end points included the average DSS and DMS during the peak GPS. AR/C symptom scores were recorded once daily in the evening in an electronic diary from the time of randomization through the end of the GPS. The DSS comprises 6 symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty eyes, and watery eyes) rated from 0 (no symptoms) to 3 (severe symptoms; eFig 2). During the GPS, subjects also used the electronic diary to record rescue medication use once daily. The DMS was composed of the sum of scores for use of rescue medications (oral antihistamines [6 points/dose], ocular antihistamines [1.5 points/drop], intranasal corticosteroids [2 points/spray], and oral corticosteroids [1.6 points/5-mg tablet for the first day of use and 3.2 points/5-mg tablet for the subsequent day(s) of use]) as shown in eFigure 2. The daily maximum DMS was 36.

Safety variables included AEs, recorded in a paper diary and inquired about during general questioning at visits. Investigators assessed AEs for severity and causality. Severity was classified as mild (awareness of sign, symptom, or event but easily tolerated), moderate (enough discomfort to cause interference with usual activity; may warrant intervention), or severe (incapacitating with inability to perform normal daily living activities or significantly affects clinical status; warrants intervention). Causality was classified as unlikely related (no temporal association, or event's cause has been identified, or drug cannot be implicated based on available information), possibly related (temporal association, but other etiologies are likely the cause; however, involvement of drug cannot be excluded based on available information), or probably related (temporal association; other etiologies are possible, but unlikely based on available information). Treatment-related AEs (TRAEs) included any AEs assessed as possibly or probably related to treatment. In accord with the Food and Drug Administration definition, a serious AE was any AE that resulted in death or was life threatening, that required hospitalization or prolonged an existing hospitalization, that resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect in offspring of a study subject (other events could be considered serious when, based on appropriate medical judgment, the event might jeopardize the subject and/or require medical or surgical intervention to prevent any of the defined serious events).

Statistical Analysis

The study was planned to randomize approximately 1,500 subjects. At the projected 17% discontinuation rate, approximately 1,240 subjects were expected to be eligible for the efficacy evaluation during the GPS. Based on the primary efficacy end point of average TCS during the entire GPS, with approximately 620 subjects per group, the study was planned to be able to detect a difference of -1.45 in the primary end point between the active dose group and the placebo group with more than 90% power at a 5% level of significance (2-sided test).

The efficacy analysis was based on a full analysis set approach, according to the intent-to-treat principle, including all subjects who received at least 1 dose of study medication and provided at least 1 efficacy measurement during the corresponding evaluation period (entire/peak GPS). Safety analysis was based on all subjects as treated (all randomized subjects who received ≥ 1 dose of study medication).

Prespecified nonparametric analyses were conducted because the data indicated a violation of the normality assumption for the planned analysis of variance method. Between-treatment comparison for the primary end point was performed using the Wilcoxon rank-sum test. The difference between 2 group medians was used to assess the absolute and relative (percent, relative to placebo) treatment difference. In addition, the Hodges-Lehmann estimator of median treatment difference and the 95% confidence interval were provided. Other TCS-, DSS-, and RQLQ-based key secondary and additional secondary end points were analyzed by the same methods. Because of the large number of 0 values in the DMS data (43.2% and 52.9% of subjects receiving placebo and MK-7243 used no rescue medication during the GPS), the average DMS over the entire and peak GPS were analyzed using a 0-inflated log-normal model with treatment, asthma status, age category (<18 or ≥ 18 years), and pollen region as covariates. The software used for statistical analysis was SAS 9.2 for UNIX (SAS Institute, Inc, Cary, North Carolina).

Planned exploratory analyses included evaluation of the primary end point in pediatric and adult subgroups using the same methods used to evaluate the primary end point in the overall population.

Multiplicity was controlled for primary and key secondary end points by using a gatekeeping sequential testing approach. Nominal *P* values were provided for other end points that were not subject to multiplicity control.

Results

Demographic and Baseline Characteristics

A total of 1,501 subjects were randomized, including 283 (18.9%) younger than 18 years; 1,498 subjects received ≥ 1 dose of study medication. Subject disposition (all randomized subjects) is shown in eFigure 3. Two subjects were randomized to placebo at baseline

Table 1
Baseline characteristics

Characteristic	Placebo (n = 749)	MK-7243 (n = 752)
Male, %	56	49
Age (y), mean	34	33
White race, %	86	82
Asthma, %	25	24
Duration of grass allergy (y)	18	17
Mean <i>Phleum pratense</i> -specific IgE (kU/L)	23	26
Timothy grass skin sensitivity, mean wheal, mm (SD)	12 (5)	12 (5)
Polysensitized, %	85	85
Sensitized to other than grass allergens (slgE ≥ 0.70 kU/L), %		
Tree	60	61
Weed	57	57
Dog	43	46
Cat	38	40
House dust mite	35	38
Sensitized to grass allergens other than timothy (slgE ≥ 0.70 kU/L), %		
Orchard	>99	>99
Kentucky bluegrass	>99	>99
Perennial rye	100	>99
Sweet vernal	100	>99
Redtop	100	>99
Johnson	88	87
Age category (y), %		
5–<12	7	8
12–<18	12	11
18–<50	66	68
50–65	15	12
≥ 65	<1	1

Abbreviation: slgE, serum immunoglobulin E.

but received MK-7243 due to medication dispensation errors; thus, these subjects were included in the MK-7243 arm for safety analysis (efficacy analysis, per intent-to-treat principles, was based on the treatment arm to which subjects were randomized). The 2 treatment groups showed similar baseline characteristics (Table 1). Of the total population, more than 99% of subjects were sensitized to related grass allergens (including orchard, Kentucky, perennial rye, sweet vernal, redtop, and/or Johnson), approximately 85% of patients were sensitized to non-grass allergens (including approximately 60% sensitized to tree pollen), and approximately 25% had concomitant asthma. A total of 1,255 (84%) randomized subjects completed the treatment period, whereas 246 subjects (16%) discontinued treatment early. The primary reasons for study discontinuation were withdrawal of consent (5% and 7% of subjects in the placebo and MK-7243 groups, respectively) and AEs (3% and 7% in the respective groups). 1,301 subjects (672 and 629 in the placebo and MK-7243 groups) who received at least 1 dose of study medication and provided at least 1 TCS measurement during the GPS were included in the primary efficacy analysis. The trial was initiated with the first patient's enrollment June 14, 2011 and concluded with the last patient's last visit on August 16, 2012.

Grass Pollen Season

The 2012 mean GPS lasted approximately 54 days; compared with historic data, the weighted (by number of subjects exposed) mean pollen count during the season of 23 grains/m³ indicated a relatively weak pollen season. The weighted mean peak-season pollen count was 53 grains/m³.

Efficacy Findings

Daily total combined score

TCS for each treatment group is plotted against daily average pollen count in Figure 1. The daily TCS generally paralleled the mean pollen counts; between-treatment differences were observed at the beginning of the GPS and throughout the season. In the analysis of the primary end point, MK-7243 yielded a reduction (improvement) vs placebo of 23% ($P < .001$) in median TCS over the

entire GPS. In addition, MK-7243 showed a 29% ($P < .001$) reduction vs placebo in median TCS over the peak GPS, when subjects tend to have the most severe symptoms and rescue medications can be expected to be most utilized (Table 2 and Fig 2).

Daily symptom score

MK-7243 yielded a 20% ($P = .001$) reduction vs placebo in median DSS over the entire GPS (Table 2 and Fig 3) and a 20% ($P < .001$) reduction in DSS vs placebo during the peak GPS. Between-group differences in the nasal and ocular components of DSS over the entire GPS also were reviewed. MK-7243 yielded reductions vs placebo of 23% ($P < .001$) and 24% ($P = .02$) in median total nasal symptom score and total ocular symptom score, respectively (Table 2).

Daily medication score

MK-7243 yielded a 35% ($P < .001$) reduction vs placebo in mean DMS over the entire GPS (Table 3 and Fig 3) and a 38% ($P < .001$) reduction vs placebo in mean DMS over the peak GPS.

RQLQ score

Five hundred twenty and 476 subjects aged >12 years in the placebo and MK-7243 groups, respectively, provided data for the RQLQ(S)12+ assessment over peak GPS. MK-7243 yielded a 12% ($P = .027$) improvement vs placebo (Table 2).

Pediatric/Adolescent and Adult Subgroups

In subjects aged 5 to <18 years ($n = 283$), MK-7243 was associated with a 32% reduction in TCS over the entire GPS vs placebo ($P = .02$). Detailed results from subgroups according to age are presented in Table 2.

Safety

Treatment with MK-7243 was generally well tolerated up to 34 weeks of treatment; the majority ($>90\%$) of AEs were assessed as mild or moderate in severity. No treatment-related serious AEs or instances of anaphylactic shock were reported. One subject receiving placebo had an event assessed by the investigator as a

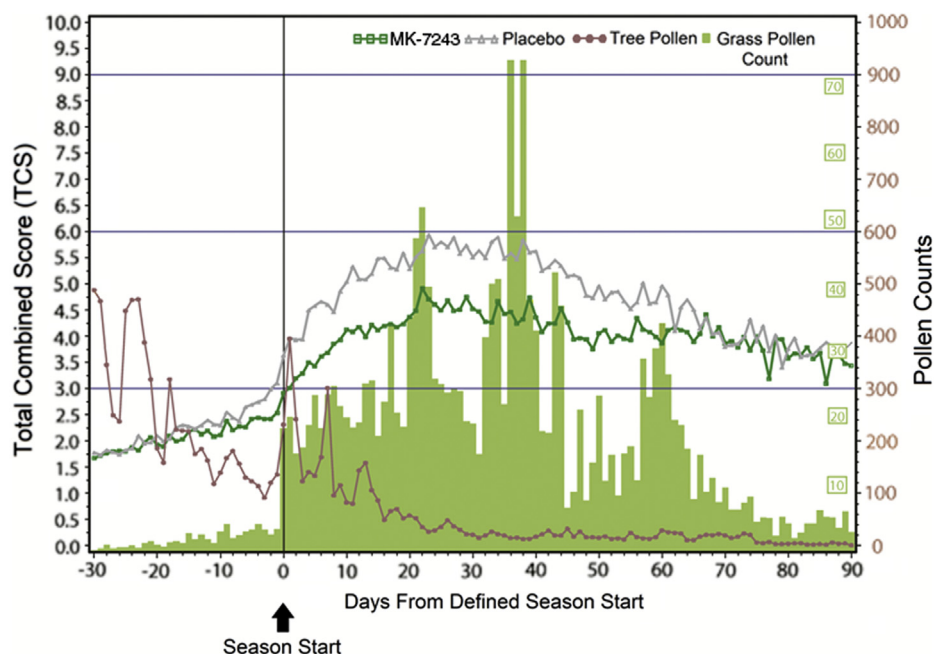


Figure 1. Mean daily total combined score and pollen count. Pollen season was defined as starting on the first day of 3 consecutive days with a grass pollen count ≥ 10 grains/m³ of air and ending on the last day of the last occurrence of 3 consecutive days with a grass pollen count ≥ 10 grains/m³ of air.

Table 2Efficacy results for TCS, DSS, TNSS, TOSS, and RQLQ(S)12+^a

	Placebo, n (median)	MK-7243, n (median)	Treatment difference (MK-7243 vs PBO)	Hodges-Lehman estimate	95% CI	P value	Difference relative to PBO estimate (%)
TCS, entire season	672 (4.22)	629 (3.24)	−0.98	−0.8	−1.2 to −0.4	<.001	−23
TCS, peak season	663 (4.67)	620 (3.33)	−1.33	−0.9	−1.4 to −0.5	<.001	−29
DSS, entire season	672 (3.13)	629 (2.49)	−0.64	−0.4	−0.7 to −0.2	.001	−20
DSS, peak season	663 (3.40)	620 (2.71)	−0.69	−0.5	−0.9 to −0.2	<.001	−20
TCS, entire season (5–<18 y old)	127 (4.09)	123 (2.77)	−1.32	−0.98	−1.9 to −0.1	.02	−32
TCS, entire season (18–65 y old)	545 (4.24)	506 (3.33)	−0.9	−0.7	−1.1 to −0.3	<.001	−21
TNSS, entire season	672 (2.30)	629 (1.76)	−0.54	−0.3	−0.5 to −0.1	<.001	−23
TOSS, entire season	672 (0.76)	629 (0.58)	−0.18	−0.1	−0.2 to 0.0	.02	−24
RQLQ(S)12+, peak season	520 (1.06)	476 (0.93)	−0.13	−0.1	−0.2 to 0.0	.027	−12

Abbreviations: CI, confidence interval; DSS, daily symptom score; PBO, placebo; RQLQ(S)12+, rhinoconjunctivitis quality-of-life questionnaire with standardized activities for subjects ≥ 12 years of age; TCS, total combined score; TNSS, total nasal symptom score; TOSS, total ocular symptom score.

^aTreatment differences (absolute and compared with placebo) are based on the difference of 2 group medians. The 95% CIs are based on the Hodges-Lehman method, and the P values are based on Wilcoxon rank-sum test.

moderate systemic allergic reaction; the subject's symptoms were treated with a β_2 agonist and an antihistamine. Two subjects receiving MK-7243 had systemic allergic reactions (both moderate in severity), with symptoms resolving without treatment. Two subjects in the MK-7243 group received epinephrine for local reactions considered related to treatment; there also were 2 epinephrine administrations for events unrelated to treatment. These events are presented in Table 4.

The most frequently reported TRAEs were local application-site reactions of the mouth, throat, and ear (primarily throat irritation, oral and/or ear pruritus, mouth edema, and oral paraesthesia; Table 5). These TRAEs were generally early-occurring, transient, and self-resolving; most local application-site reactions occurred within the first week of treatment.

Severe AEs were experienced by 5% and 9% of subjects in the placebo and MK-7243 arms, respectively (7% of all AEs during the treatment period were assessed as severe). Severe TRAEs were experienced by 8 of 745 (1%) and 23 of 753 (3%) subjects in the placebo and MK-7243 groups, respectively; most ($n = 19$) severe TRAEs in subjects taking MK-7243 were local application-site reactions. Two percent and 7% of subjects in the placebo and MK-7243 arms, respectively, discontinued due to AEs; 1% and 6% of

subjects in these groups discontinued due to TRAEs. Discontinuations due to treatment-related local application-site reactions typically occurred within the first several weeks of treatment.

Safety findings were comparable among age groups, with similar percentages of subjects among all age groups experiencing AEs. No new safety signals emerged. In all groups, AEs were primarily local application-site reactions and no safety signal in subjects with asthma was apparent (overall, TRAEs were reported for 43.2% and 40.7% of asthmatic and non-asthmatic subjects).

Discussion

The results of this trial showed MK-7243 to be associated with significant decreases in TCS and its components, DMS and DSS, vs placebo. Results of this trial are consistent with previous research, including 2 previous North American randomized, placebo-controlled trials of MK-7243, which included smaller study populations.^{10,11} Among 345 North American children and adolescents studied by Blaiss et al,¹⁰ MK-7243 significantly decreased entire-season TCS by 26% vs placebo; among 439 North American adults studied by Nelson et al,¹¹ MK-7243 significantly decreased entire-season TCS by 20% vs placebo. These 2 trials and the present

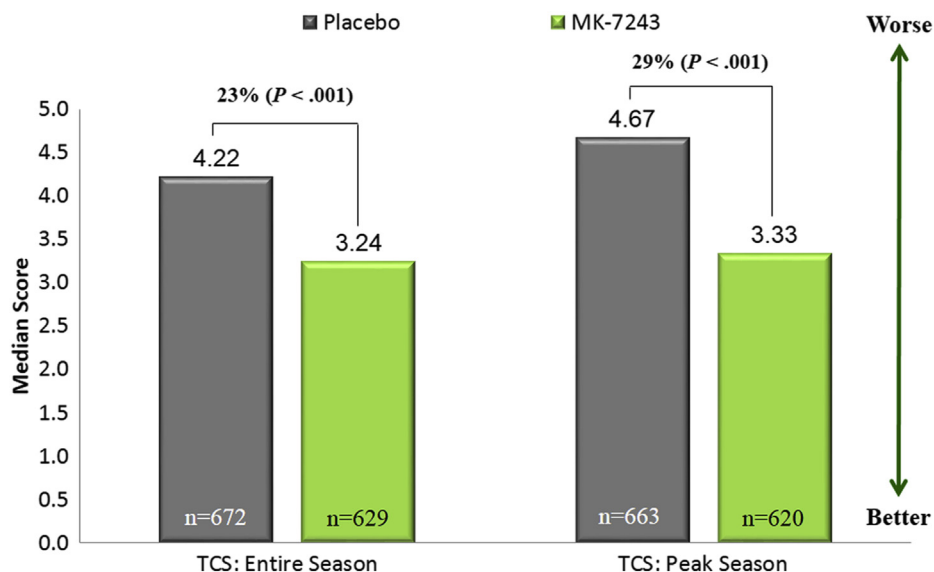


Figure 2. Total combined score (TCS) over the entire and peak grass pollen season. The 95% confidence intervals for percentage reduction for MK-7243 vs placebo were 13% to 36% in median TCS over the entire grass pollen season and 15% to 39% in median TCS over the peak grass pollen season. Between-treatment differences for MK-7243 vs placebo were −0.98 over the entire grass pollen season and −1.33 over the peak grass pollen season.

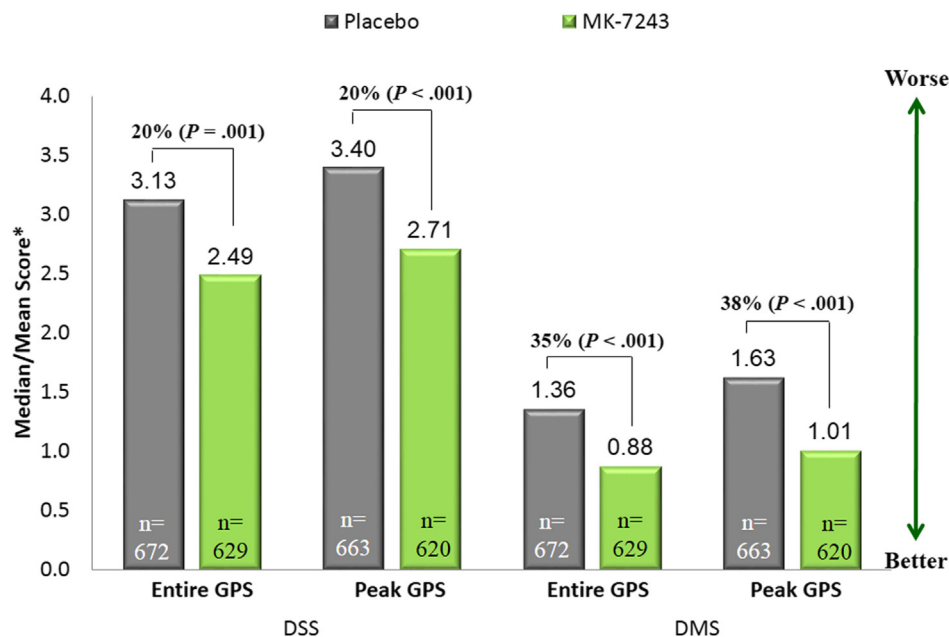


Figure 3. Daily symptom score (DSS) and daily medication score (DMS) over the entire and peak grass pollen season (GPS). *Medians are reported for DSS, and means are reported for DMS (see “Statistical Analysis” section). Between-treatment differences in DSS for MK-7243 vs placebo were -0.64 over the entire GPS and -0.69 over the peak GPS. Between-treatment differences in DMS for MK-7243 vs placebo were -0.48 over the entire GPS and -0.62 over the peak GPS.

study contrast with a previous North American trial of MK-7243 (GT-14) that did not meet its primary end point (DSS over the entire GPS).¹⁷ Considering the efficacy seen in the present trial despite a relatively weak pollen season, and its large-scale replication of the results reported by Nelson et al¹¹ and Blaiss et al,¹⁰ the accumulated data provide strong evidence of the efficacy of treatment with MK-7243 in North American children and adults with grass pollen–induced AR/C. When European trials are included, the efficacy of MK-7243 has been demonstrated in trials including more than 850 children/adolescents and 3,500 adults. In contrast to MK-7243, treatment with oral antihistamines alone, such as the loratadine allowed in the present study, has been shown to reduce grass pollen AR/C symptoms by only 8% compared with placebo.¹⁸ Therefore, MK-7243 provides an effective oral treatment for grass pollen–induced AR/C with the potential for disease modification, as demonstrated in the European trial GT-08.¹⁹

The safety results observed in this study showed that most AEs were self-limiting, mild or moderate local application-site reactions. The events typically lessened or disappeared with repeated treatments, and there were no severe systemic allergic events reported. The 2 events assessed as moderate systemic reactions occurring in the MK-7243 arm progressed slowly and resolved without medical intervention or pharmacologic treatment. It is noteworthy that 1 subject in the placebo group was treated for an event assessed as a moderate anaphylactic reaction.

The AE profile observed in this trial provides further confirmation corresponding to the evidence-based World Allergy Organization and Allergic Rhinitis and its Impact on Asthma

characterization of sublingual immunotherapy as sufficiently well tolerated to permit at-home administration.^{8,20} Epinephrine was used by 2 subjects taking MK-7243 subjects for symptoms that were assessed as unrelated to the study medication, and by 2 subjects for a related MK-7243 local event. Of the epinephrine usage in response to TRAEs, both occurred in the absence of indications of respiratory compromise/hypotension or other symptoms described by World Allergy Organization guidelines as suggestive of acute anaphylaxis.²¹ Other trials of MK-7243 have included previous North American trials in which the first 3 doses were administered under supervision and European trials in which only the first dose was given under supervision (as in the present study), with no evident safety differences between the 2 schedules.^{10–13} The present study also showed that the same 2,800-BAU MK-7243 dosage was well tolerated without up-titration by subjects in the adult and pediatric subgroups, as suggested by the use of this dose regimen in previous separate trials in adult and pediatric populations.^{10–13} Therefore, the practices of initiating sublingual tablet use at the maintenance dosage with a single in-office administration, as well as not adjusting the dosages of immunotherapy for age or weight, are supported by the present data and those from prior trials.^{10–13}

The mean grass pollen count observed in this study was 23 grains/m³, indicating a weak pollen season compared with the average peak grass pollen observed in other trials in which counts in the northeastern United States have reached more than 100 grains/m³.²² Nevertheless, mean DMS was 35% higher with placebo vs MK-7243 over the entire GPS, indicating a substantial reduction

Table 3
Efficacy results for DMS^a

	Placebo, mean (n)	MK-7243, mean (n)	Treatment difference (MK-7243–PBO)	95% CI	P value	Difference relative to PBO (%) estimate
DMS, entire season	1.369 (672)	0.88 (629)	–0.48	–0.7 to –0.2	<.001	–35
DMS, peak season	1.63 (663)	1.01 (620)	–0.62	–0.9 to –0.3	<.001	–38

Abbreviations: CI, confidence interval; PBO, placebo; DMS, daily medication score.

^aTreatment differences (absolute and relative to placebo), 95% CIs, and P values are based on a 0-inflated log-normal model with treatment, asthma status, age category (<18 or ≥18 y), and pollen region as covariates.

Table 4

Details of systemic reactions and epinephrine use

Treatment (age/sex)	Day of dosing: symptoms	Assessment as determined by investigator/outcome
Systemic reactions		
Placebo (13/M)	Day 1: symptoms of wheezing, cough, and increased nasal congestion within 10 min of first dose (subject had mild asthma); vital signs normal. Subject was treated with a β_2 agonist and an antihistamine; symptoms resolved.	Assessed as moderate anaphylactic reaction. Subject discontinued.
MK-7243 (22/M)	Day 15: throat tightness lasting approximately 5 min. AEs worsened over several weeks; subject began experiencing tongue edema. Day 42: chest tightness and shortness of breath after taking study medication. Symptoms resolved over 30 min without treatment.	Assessed as moderate systemic allergic reaction. Subject discontinued.
MK-7243 (45/F)	Day 2: edema on lower lip, redness on corners of mouth and chin, epigastric discomfort, and dizziness. Symptoms resolved after 1 h without medical intervention or treatment.	Assessed as moderate systemic allergic reaction. Subject discontinued.
Epinephrine use		
Placebo (52/M)	Approximately 1.5 mo after trial enrollment: hospitalized due to an episode of lightheadedness and unresponsiveness (had been experiencing fatigue, myalgia, and rhinorrhea during an URTI over several weeks; had developed generalized urticaria and lip angioedema). Epinephrine administered for initial symptoms and for subsequent event of syncope during hospitalization.	Symptoms attributed to an urticarial vasculitis, confirmed by skin biopsy; assessed as life threatening, unrelated to study medication.
MK-7243 (36/M)	Day 1: mild local tingling. Day 2: mild sublingual swelling after dosing; 12 h later developed rash, shortness of breath, throat tightness, and "heaviness" of tongue; self-administered epinephrine and antihistamine. Day 3: self-administered MK-7243 (no AE). Day 4: received MK-7243 at investigator's office; mild local tingling.	Subject realized he had been exposed to bed bugs. Final diagnosis: idiopathic urticaria/bug bites and anxiety; unrelated to study medication.
MK-7243 (18/M)	Day 3: irritation and swelling in throat, without difficulty breathing or swallowing. Subject administered epinephrine but did not tell parent or seek medical attention; he discontinued from the trial. Approximately 1 mo later, the subject reported event at early termination visit.	Throat irritation and swelling assessed as severe, possibly related to study medication.
MK-7243 (65/F)	Over the first weeks of dosing: worsening of pruritus around the mouth and throat irritation. Day 14: within 15 min of dosing, local reaction developed. The event was not rapidly progressing and the subject drove to the investigational site, where she presented with throat tightness, lip and facial swelling on the left side, rhinorrhea, and a hoarse voice. Lungs were clear, vital signs were normal. Epinephrine (approximately 1 h after study drug dosing) and antihistamine were administered.	Assessed as moderate local hypersensitivity reaction probably related to study medication; subject discontinued.

Abbreviations: AE, adverse event; M, male; F, female; URTI, upper respiratory tract infection.

in the need for symptomatic rescue medication among those receiving active treatment. The use of rescue medication also may explain the low DSS in placebo-treated subjects.

Also of note is the fact that the tablet with extract of timothy grass only was observed to be effective despite the fact that virtually all subjects were sensitized to cross-reactive northern pasture grasses and 85% of subjects also were sensitized to non-grass allergens, including tree pollen. This is consistent with previous clinical trials of MK-7243 with large proportions of polysensitized subjects. In addition, these findings lend support to the guidance from the Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology immunotherapy practice parameters, which state that the use of a representative member from the temperate pasture grass family generally provides efficacy against the entire group.⁷ The data suggest that a single-grass timothy grass sublingual allergy immunotherapy tablet is sufficient for treating patients with timothy and related grass sensitizations.

Recent results from the Allergies, Immunotherapy, and Rhinoconjunctivitis Patient Survey (including 2,765 respondents ≥ 5 years old with a professional diagnosis of "hay fever," AR, AR/C, or nasal or eye allergies, and symptoms or medication for the condition in the previous 12 months) indicate that nasal and ocular

symptoms cause distress to patients with allergy.²³ Further, nasal and ocular allergic symptoms have been shown to negatively affect quality of life.²⁴ Therefore, optimal AR/C therapy would effectively relieve nasal and ocular symptoms; in the present study, MK-7243 alleviated nasal and ocular symptoms by similar percentages (23% and 24%, respectively). These reductions also were accompanied by a 12% improvement vs placebo in quality of life according to the RQLQ(S)12+, although it must be acknowledged this scale was originally designed for and validated in trials of symptomatic pharmacotherapy as a change-from-baseline measurement, not in immunotherapy trials in which seasonal scores are compared directly, and that such quality-of-life measurements do not account for the use of rescue medications in immunotherapy trials.^{25,26}

Long-term disease modification cannot be ascertained from this trial given its duration. Previously conducted research in European subjects receiving MK-7243 found a persistent reduction in symptoms assessed 2 years after the conclusion of a 3-year period of continuous daily treatment. Two years after treatment, subjects who had received MK-7243 continued to have significantly lower symptom scores, medication scores, and combined scores during the GPS vs subjects in the placebo arm.¹⁹ The treatment duration used to achieve this disease-modifying effect was consistent with the duration that appears to be necessary for disease modification with subcutaneous allergy immunotherapy.²⁷

In conclusion, in the largest immunotherapy trial yet conducted, MK-7243 was effective in polysensitized grass-allergic North American children and adults with AR/C. MK-7243, self-administered at home after a single office visit administration, generally was well tolerated; most AEs were local application-site reactions, and there were no serious TRAEs in the 1,501 subjects enrolled. The study confirms results from previous trials, which indicated that once-daily MK-7243 is well tolerated and effective in children and adults, further contributing to the accumulated evidence supporting the efficacy and safety of this form of therapy.

Table 5

Most commonly reported TRAEs

TRAE, n (%)	Placebo (n = 745)	MK-7243 (n = 753)
Any TRAE	178 (23.9)	441 (58.6)
Throat irritation	26 (3.5)	175 (23.2)
Oral pruritus	20 (2.7)	139 (18.5)
Oral paresthesia	23 (3.1)	90 (12.0)
Mouth edema	9 (1.2)	98 (13.0)
Ear pruritus	11 (1.5)	91 (12.1)

Abbreviation: TRAE, treatment-related adverse event.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.11.008>.

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eMethods

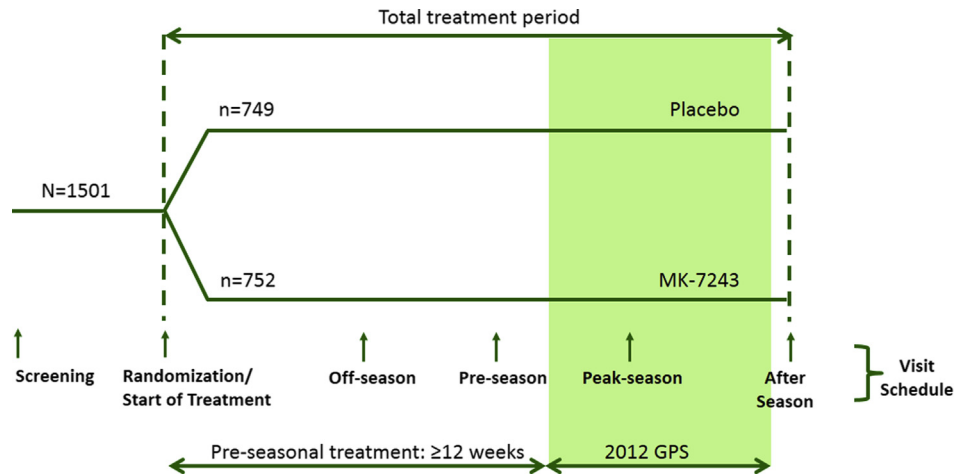
Additional Inclusion Criteria

Subjects were required to have an electrocardiogram reading at screening that was within normal limits or clinically acceptable, and to be willing to give informed consent, and able to adhere to dose and visit schedules (subjects under the age of legal consent were required to give assent, and their parents/guardians were required to give legal consent). Subjects (or their parent/guardian) participating in exploratory pharmacogenetic analysis were required to give written informed assent. Female subjects of child-bearing potential were required to provide a negative pregnancy test result at screening and remain abstinent or use 2 acceptable methods of birth control during treatment.

Additional Exclusion Criteria

Subjects were excluded if they were breast-feeding, pregnant, or intending to become pregnant; were receiving ongoing specific

immunotherapy at screening; had a history of allergy, hypersensitivity, or intolerance to ingredients of the study drug (except for *Phleum pratense*), rescue medications, or self-injectable epinephrine; had a history of anaphylaxis with cardiorespiratory symptoms, self-injectable epinephrine use, or chronic urticaria and angioedema; a history of chronic sinusitis during the previous 2 years; had current severe atopic dermatitis; had any clinically significant condition or situation that, in the opinion of the investigator, would interfere with study evaluations or optimal participation; had received any investigational drug within 30 days of screening; were participating or planned to participate in another clinical study; were family of the study staff; were unable to meet medication washout requirements; were unlikely to complete the trial or were likely to travel for extended periods during the GPS; or had a clinically significant abnormal vital sign or laboratory value that, in the opinion of the investigator, would preclude participation in the study. Subjects could not participate in the study at multiple sites or be randomized into the study more than once.



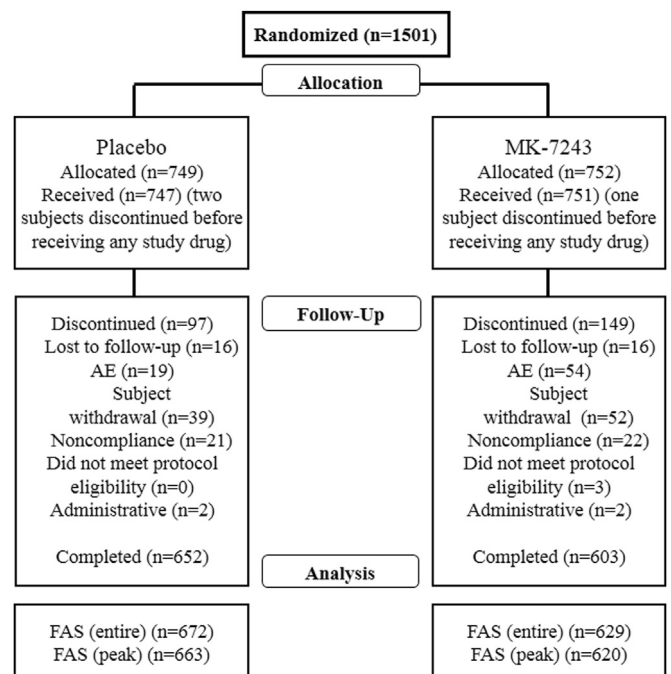
eFigure 1. Study design. GPS, grass pollen season.

Daily TCS: DSS + DMS

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

DMS, Maximum=36		
Rescue Medication	Score/Dose Unit	Maximum Daily Score
Loratadine ^a	6 points/dose	6
Olopatadine HCl 0.1% ophthalmic solution ^b	1.5 points/drop	6
Mometasone furoate nasal spray 50 µg ^c	2 points/spray	8
Prednisone 5-mg tablet ^d	1.6 points/tablet	16

eFigure 2. Symptom and medication use scoring. ^aLoratadine was given as 5 mL of Claritin (Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey) in 1 mg/mL of syrup every day (QD) for subjects 5 to <6 yr, 10 mg in 1 mg/mL of Claritin syrup QD for subjects ≥6 to 18 yr, or 1 Claritin RediTabs tablet 10 mg QD for subjects ≥6 yr; could be used during the grass pollen season when the daily symptom score (DSS) was ≥4. ^bOlopatadine (Patanol; Alcon, Hünenberg, Switzerland) could be used in addition to loratadine for control of persistent eye symptoms. ^cMometasone furoate (Nasonex; Merck Sharp & Dohme Corp) given at 1 spray/nostril QD for subjects 5 to <12 years; 2 sprays/nostril QD for subjects ≥12 years; could be used when the DSS ≥4 despite loratadine use. ^dPrednisone (West-Ward Pharmaceuticals, Lionville, Pennsylvania) day 1, 1 mg/kg/d, maximum 50 mg/d, 1.6 points/tablet; subsequent days 0.5 mg/kg/d, maximum 25 mg/d, 1.6 points × 2/tablet; could be used when the DSS ≥4 despite loratadine and mometasone furoate use. DMS, daily medication score; TCS, total combined score.



eFigure 3. Subject disposition. Some subjects discontinued after providing diary entry during the grass pollen season and thus are included in “discontinued” and “FAS.” AE, adverse event; FAS, full analysis set.