

Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber

Hendrik Nolte, MD, PhD,^a Jennifer Maloney, MD,^a Harold S. Nelson, MD,^b David I. Bernstein, MD,^c Susan Lu, PharmD,^a Ziliang Li, PhD,^a Amarjot Kaur, PhD,^a Petra Zieglmayer, MD,^d René Zieglmayer, Dipl Ing,^d Patrick Lemell, PhD,^d and Friedrich Horak, MD^d Kenilworth, NJ, Denver, Colo, Cincinnati, Ohio, and Vienna, Austria

Background: The magnitude of effect of sublingual immunotherapy for house dust mite (HDM)–induced allergic rhinitis with or without conjunctivitis is uncertain, partly because there are few well-controlled trials with well-defined doses.

Objective: We sought to determine the dose-related efficacy and onset of action of the HDM sublingual immunotherapy tablet MK-8237 (Merck/ALK-Abelló) using the Vienna Challenge Chamber.

Methods: In this randomized, double-blind, single-site trial, adults with HDM-induced allergic rhinitis with or without conjunctivitis and with or without asthma ($n = 124$) received 12 developmental units (DU) of MK-8237, 6 DU of MK-8237, or placebo daily for 24 weeks. Subjects underwent 6-hour exposure challenges at screening and weeks 8, 16, and 24. The total nasal symptom score (TNSS) during chamber challenge at week 24 was the primary end point. The TNSS was the sum of 4 nasal symptom scores (maximum = 12). Total ocular symptom scores (TOSSs; 2 symptoms; maximum = 6) and total symptom scores (TSSs; TSS = TNSS plus TOSS; maximum = 18) were secondary end points.

Results: Dose- and time-dependent improvements with MK-8237 versus placebo were observed. At week 24, TNSS improvement relative to placebo was 48.6% (95% CI, 35.3% to 60.2%) with 12 DU of MK-8237 and 26.6% (95% CI, 11.2% to 39.6%) with 6 DU of MK-8237. Statistically significant improvements for TNSSs were also observed at weeks 8 (12 DU of MK-8237) and 16 (6 and 12 DU of MK-8237) and for TOSSs and TSSs by both doses at week 24. MK-8237 was well tolerated.

No investigator-assessed anaphylactic allergic reactions or reactions requiring epinephrine were observed.

Conclusions: MK-8237, 12 DU, reduced nasal and ocular symptoms and exceeded World Allergy Organization–established clinical efficacy criteria ($\geq 20\%$ improvement vs placebo). The onset of action for 12 DU of MK-8237 was week 8. MK-8237, 12 DU, is appropriate for further evaluation to determine the magnitude of effect in an uncontrolled allergen exposure environment. (J Allergy Clin Immunol 2015;■■■:■■■–■■■.)

Key words: Allergen immunotherapy, allergic rhinoconjunctivitis, house dust mite, sublingual immunotherapy tablet, dose response, dose related, onset of action, environmental exposure chamber, nasal symptoms, ocular symptoms

Subcutaneous immunotherapy (SCIT) has been demonstrated to decrease symptoms associated with house dust mite (HDM)–induced allergic rhinitis (AR).^{1–3} However, SCIT requires frequent office visits, which might be inconvenient for many patients. Indeed, inconvenience is the most common reason for a patient to discontinue or reject SCIT.⁴ Alternatively, sublingual immunotherapy (SLIT) has been investigated as a simple and favorable form of immunotherapy with a potentially more benign safety profile.⁵ However, a review of HDM SLIT studies concluded that reported results have been variable, partly because of insufficient treatment exposure, and there is a need for more rigorous studies that assess standardized efficacy outcomes, treatment duration, and dose.⁶ Few dose-finding or onset-of-action studies have been conducted for perennial allergens in general, let alone HDM.⁷ Thus, there is limited knowledge regarding dose responses and onset of action with HDM SLIT.

The magnitude of the efficacy of immunotherapy is related to environmental allergen exposure; when allergen exposure is high, a greater treatment effect with SLIT is observed.⁸ The environmental exposure chamber (EEC) provides an efficient method to optimize exposure and reduce confounding from nonspecific triggers or overlapping allergens.^{9,10} Thus, compared with field trials, EEC studies allow for a better assessment of the dose response, onset of action, and potentially the optimal magnitude of the treatment effect of immunotherapy products. Because of the controlled environment of the EEC, there is very low variability in outcomes, which can lead to highly significant results with a smaller sample size than what is required for field studies.⁹ Furthermore, a strong correlation between symptoms experienced during controlled exposure and in-field allergen exposure has been demonstrated.¹¹ As such, an EEC study was conducted to determine the appropriate dose for further field trial evaluation of the rapidly dissolving (within seconds) HDM SLIT tablet

From ^aMerck & Co, Kenilworth; ^bthe Department of Medicine, Division of Allergy and Immunology, National Jewish Health, Denver; ^cthe Bernstein Allergy Group and the Division of Allergy and Immunology, University of Cincinnati, Cincinnati; and ^dVienna Challenge Chamber, Vienna.

Supported by Merck & Co.

Disclosure of potential conflict of interest: This study was funded by Merck & Co. H. Nolte is employed by Merck, as is J. Maloney, S. Lu, Z. Li, and A. Kaur. H. S. Nelson has received consulting fees or honorariums from Merck, as well as consultancy fees from Circassia, from which he has also received or has grants pending. D. I. Bernstein has received consultancy fees from Merck and Circassia, as well as payment for delivering lectures from Merck, and has received or has grants pending from Merck and Circassia. F. Horak holds several international patents from Europe, Canada, and the United States, pertaining to a fundamental technique of the allergen challenge chamber. The rest of the authors declare that they have no relevant conflicts of interest.

ClinicalTrials.gov identifier: NCT01644617.

Received for publication September 22, 2014; revised November 25, 2014; accepted for publication December 16, 2014.

Corresponding author: Hendrik Nolte, MD, PhD, Merck & Co, 1 Merck Dr, Whitehouse Station, NJ 08889. E-mail: Hendrik.nolte@merck.com.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2014.12.1911>

Abbreviations used

AAR:	Active anterior rhinomanometry
AE:	Adverse event
AR:	Allergic rhinitis
AR/C:	Allergic rhinitis with or without conjunctivitis
DU:	Developmental units
EEC:	Environmental exposure chamber
HDM:	House dust mite
MID:	Minimally important difference
RQLQ(S)12+:	Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for subjects ≥ 12 years old
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
TNSS:	Total nasal symptom score
TOSS:	Total ocular symptom score
TSS:	Total symptom score
VAS:	Visual analog scale
VCC:	Vienna Challenge Chamber

MK-8237 (Merck & Co, Kenilworth, NJ, and ALK-Abelló, Hørsholm, Denmark). Prior dose-escalation safety and tolerability trials with MK-8237 tested up to 32 developmental units (DU) per dose and demonstrated that doses of up to 12 DU of HDM SLIT tablet were tolerated and thus suitable for further clinical efficacy evaluations.¹²

The primary objective was to characterize the dose-related efficacy of MK-8237 versus placebo based on the total nasal symptom score (TNSS) at week 24 in subjects with HDM-induced allergic rhinitis with or without conjunctivitis (AR/C) and with or without asthma. Onset of action was a key secondary objective.

METHODS

Study design

This was a randomized, placebo-controlled, double-blind, dose-ranging, onset-of-action, single-site trial (Vienna Challenge Chamber [VCC] Site, Vienna, Austria) conducted between October 29, 2012, and August 27, 2013. The challenge sessions during the trial were conducted outside of the regional tree and grass pollen seasons to avoid having subjects who were symptomatic to other environmental allergens at the time of the efficacy assessments. The clinicaltrials.gov identifier was NCT01644617.

The VCC is a 54-m³ sealed room in which a precisely defined and monitored airborne concentration of HDM allergen (approximately 0.3 g of material per hour) was administered to subjects continuously and maintained over a period of 6 hours per challenge visit. The VCC was charged with 100% fresh air which was cleaned, cooled, dried, and then loaded with the qualitatively and quantitatively determined HDM allergen load. The house dust material was a 10:10:1 mixture of *Dermatophagoides pteronyssinus* whole bodies, *Dermatophagoides farinae* whole bodies, and feces from both species, which reflects the composition of mite material during natural exposure.^{13,14} Challenge visits occurred during the screening period and at weeks 8, 16, and 24 of treatment. Office visits without exposure challenge occurred at weeks 4, 12, 20, and 26 (Fig 1).

This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by an independent ethics committee, and written informed consent was obtained from each subject before the study.

Treatment

Adults with a history of HDM-induced AR/C with or without asthma were randomized 1:1:1 according to a computer-generated randomization schedule

to 12 DU of MK-8237, 6 DU of MK-8237, or placebo daily for approximately 24 weeks (Fig 1). Randomization numbers were assigned to subjects by providing the next available number and kit (ordered sequentially). Placebo and MK-8237 were identical in appearance, smell, taste, and packaging to ensure treatment blinding was maintained. The sponsor, investigator, study personnel, and study subjects were blind to treatment. DU is a measure of the potency of the tablet based on an in-house reference used to standardize the HDM extracts during development of MK-8237. In Europe the DU is referred to as the SQ-HDM. MK-8237 contains a 1:1 mixture of *D pteronyssinus* and *D farinae* characterized by a constant ratio between the 4 major allergens: *D pteronyssinus* group 1 and group 2 allergens and *D farinae* group 1 and group 2 allergens. The first dose was self-administered on site, and subjects were monitored for 30 minutes after tablet intake. Subsequent doses were self-administered at home. The tablet was to be placed under the tongue and allowed to remain for a few seconds until dissolved. Subjects were advised not to swallow during the first minute after administration. Treatment compliance was assessed by subject-reported compliance and inspection of study drug at monthly visits and was calculated as the number of days on the study drug divided by the number of expected days on the study drug. A washout period of 3 days before randomization and before each exposure challenge was required for antihistamines and decongestants; the use of oral, nasal, or ocular corticosteroids was not permitted during the trial. Self-injectable epinephrine is not a requirement for SLIT studies in Europe and was therefore not prescribed.

Key inclusion and exclusion criteria

Subjects eligible for inclusion in the trial were men and women aged 18 years or older with HDM-induced AR/C of 1 year or longer in duration with or without asthma. Subjects were required to have a TNSS of 6 or more of a possible 12 within the first 2 hours of the screening exposure challenge; a positive skin prick test response (wheal diameter ≥ 3 mm larger than saline control) to *D pteronyssinus*, *D farinae*, or both at screening; a serum specific IgE level (≥ 0.7 kU/L equivalent to RAST class 2 or greater) to *D pteronyssinus*, *D farinae*, or both at screening; and an FEV₁ of 70% of predicted value or greater (according to reference values of the European Coal and Steel Community) at screening and randomization. Subjects were excluded from the trial if they had unstable, uncontrolled/partially controlled, or severe asthma as judged by the investigator; asthma requiring medium- or high-dose inhaled corticosteroids within the last 12 months before screening; or HDM immunotherapy within the past 3 years. Key discontinuation criteria were as follows: a life-threatening treatment-related adverse event (AE); a decrease in FEV₁ of 20% or peak expiratory flow of 25% less than prechallenge values during the exposure challenge; a late-phase asthmatic reaction temporally associated with exposure challenge that required treatment and, per the investigator's discretion, necessitated discontinuation; poor asthma control despite titration of inhaled corticosteroids based on the investigator's assessment; and a treatment-related acute severe asthmatic reaction or anaphylactic reaction.

Study assessments

Symptoms were scored every 15 minutes during exposure challenges and recorded directly in an electronic database. It was expected that symptoms during exposure challenges would plateau after about 2 hours.^{15,16} Thus, data collected from the last 4 hours of each 6-hour challenge were used to derive the symptom-based efficacy end points. A total of 9 nasal, ocular, and asthma symptoms were evaluated, and each was scored as 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), or 3 (severe symptoms, see Table E1 in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org). Nasal symptoms were runny nose, blocked nose, sneezing, and itchy nose; ocular symptoms were gritty/red/itchy eyes and watery eyes; and asthma symptoms were cough, wheeze, and dyspnea.

The primary efficacy end point was the average TNSS at week 24. The TNSS was the sum of the 4 nasal symptoms, with a maximum score of 12 (see Table E1). Key secondary efficacy end points were the average TNSS at weeks 8 and 16 and the average total symptom score (TSS) at week 24. The TSS was the sum of the 4 nasal symptoms and 2 ocular symptoms, with a maximum

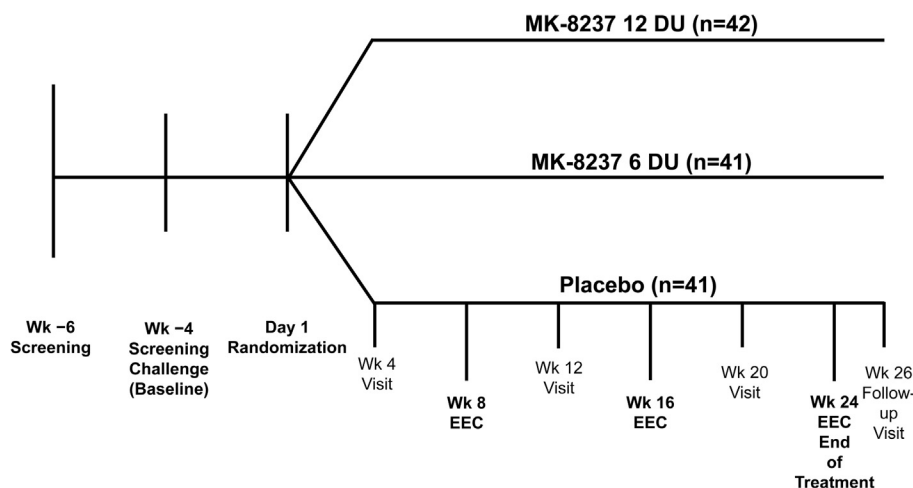


FIG 1. Study design.

score of 18 (see Table E1). Other secondary efficacy end points were the average TSS at weeks 8 and 16 and the average total ocular symptom score (TOSS) at weeks 8, 16, and 24. The TOSS was the sum of the 2 ocular symptoms, with a maximum score of 6 (see Table E1). HDM-specific serum IgE and IgG4 levels at week 8, as well as change from screening to week 8, were also secondary end points. Immunologic data at week 24 were collected and assessed *post hoc* from a subset of subjects who signed the future biomedical research consent form. A key secondary objective of the study was to determine the onset of action of MK-8237. Onset of action was defined as the first time point that the difference in TNSS between MK-8237 treatment and placebo was statistically significant.

Exploratory end points were the asthma symptom score (maximum = 9), the prechallenge Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for subjects ≥ 12 years old (RQLQ[S]12+) score, prechallenge rhinoconjunctivitis symptoms assessed by using a visual analog scale (VAS), and change from prechallenge active anterior rhinomanometry (AAR). The RQLQ(S)12+ and VAS were conducted at randomization and before challenge at weeks 8, 16, and 24. For the VAS, subjects rated symptoms over the previous 7 days on a 10-cm scale, scoring symptoms from “no symptoms” (0 points) to “severe symptoms” (100 points). The purpose of evaluating the RQLQ(S)12+ and VAS results at the randomization visit and before entering the exposure challenges was to explore the overall treatment effect of the study drug over the entire trial period outside of the challenge setting. AAR was conducted at screening and weeks 8, 16, and 24 and was conducted approximately 30 minutes before each exposure challenge and every 30 minutes during each challenge session.

Safety evaluation included reporting of AEs, which were graded for severity and relationship to study drug by the investigator. Vital signs and laboratory assessments were also monitored. Safety analyses were performed for all randomized subjects who took 1 or more doses of study drug.

Statistical analysis

The study was designed to enroll approximately 132 subjects with an assumed discontinuation rate of 10% and to have 80% power to detect (2-sided, $\alpha = .050$) a difference of 2.0 units in the average TNSS at week 24 between active treatment and placebo with an assumed SD of 3.2. Efficacy analyses were performed on all randomized subjects who took 1 or more doses of study drug with 1 or more postrandomization efficacy measurements (full analysis set). All analyses were performed based on observed data only. The primary analysis was based on the analysis of covariance parametric model by using treatment and baseline values as covariates. Baseline values were based on scores at the screening challenge. For the primary end point, multiplicity was controlled by using a step-down procedure in which the comparison between 12 DU of MK-8237 and placebo was conducted first. Least square means estimated from the

analysis of covariance model were used to determine the percentage treatment difference relative to placebo, which was calculated as follows:

$$(\text{MK-8237} - \text{Placebo}) / \text{Placebo} \times 100\%.$$

Key secondary and other secondary end points were assessed by using the same model as the primary end point. Immunologic and exploratory end points were analyzed by means of ANOVA, with treatment as a fixed effect. Statistical analyses were conducted with SAS version 9.3 software (SAS Institute, Cary, NC).

RESULTS

Subjects

Of the 153 subjects screened, 124 were randomized and received at least 1 dose of study drug; 106 subjects completed the study (see Fig E1 in this article's Online Repository at www.jacionline.org). Reasons for discontinuation were AEs ($n = 9$ [7.3%]), withdrawal by subject ($n = 8$ [6.5%]), and loss to follow-up ($n = 1$ [0.8%]). All 124 randomized subjects were included in the safety analysis, and 119 subjects were included in the efficacy analyses.

Demographic and clinical characteristics were generally well balanced among treatment groups at screening, although a higher percentage of subjects in the 6-DU group were women (Table I). A total of 86.3% of subjects were polysensitized to allergens other than HDM (Table I); the most predominant allergen sensitivities other than HDM were timothy grass (71.8%), birch (53.2%), and cat and dog dander (each 49.2%, Table I). A total of 24.2% of subjects reported a history of asthma. TNSSs and TOSSs were generally comparable among all treatment groups at screening (Table I). Compliance with study drug was similar among the treatment groups, with means ranging from 97.5% to 98.8%.

Efficacy assessments

A dose- and time-dependent effect of MK-8237 on TNSSs was observed (Fig 2, A). At week 24 (primary efficacy evaluation time point), the improvement in TNSSs relative to placebo was 48.6% (95% CI, 35.3% to 60.2%) with the 12-DU dose and 26.6% (95% CI, 11.2% to 39.6%) with the 6-DU dose. The mean differences in TNSSs versus placebo at week 24 were significant for both the 12-DU and 6-DU doses (Table II). Significant improvements in

TABLE I. Baseline demographics and clinical characteristics

	MK-8237, 12 DU (n = 42)	MK-8237, 6 DU (n = 41)	Placebo (n = 41)
Women, no. (%)	19 (45)	30 (73)	17 (42)
Age (y)			
Mean	28	27	27
Range	18-58	20-48	19-43
White, no. (%)	37 (88)	38 (93)	38 (93)
Subjects with asthma, no. (%)	10 (24)	11 (27)	9 (22)
ICS use, no. (%)	4 (10)	1 (2)	1 (2)
Mean duration of AR/C (y)	16	16	17
IgE sensitization type, no. (%)			
HDM only	5 (12)	4 (10)	7 (17)
HDM and other allergens	37 (88)	37 (90)	34 (83)*
Birch tree	22 (52)	24 (59)	20 (49)
Timothy grass	28 (67)	32 (78)	29 (71)
Cat dander	19 (45)	23 (56)	19 (46)
Dog dander	20 (48)	22 (54)	19 (46)
TNSS at screening†	7.82	8.06	7.41
TOSS at screening†	1.94	2.34	1.94

ICS, Inhaled corticosteroid.

*One subject did not have an HDM serum-specific IgE level of 0.7 kU/L or greater to either species at screening; however, retesting after randomization demonstrated an HDM-induced allergic response. This subject demonstrated an allergic response to other allergens (was polysensitized) at screening.

†Average score during the last 4 hours of the screening challenge session based on subjects in the full analysis set population.

TNSSs relative to placebo were also observed at week 8 (the earliest time point measured) and week 16 for the 12-DU dose and at week 16 for the 6-DU dose (Fig 2, A, and Table II).

The average TNSS over time during the exposure challenge at week 24 is shown in Fig 3. A sustained separation of subject response across the treatment groups was observed at each time point after the first hour of challenge. The separation between the 12-DU dose and placebo was significant at every time point. When average TNSSs over time during each exposure challenge were examined, the 12-DU dose continued to improve during the course of the study, suggesting a longer dosing period might result in an even greater effect (see Fig E2 in this article's [Online Repository](#) at [www.jacionline.org](#)).

The proportion of randomized subjects who reported ocular symptoms at the screening chamber challenge was 61.9%, 63.4%, and 75.6% for the 12-DU, 6-DU, and placebo groups, respectively (71% overall); a dose- and time-dependent effect of MK-8237 was observed for TOSSs (Fig 2, B). Significant improvements in TOSSs relative to placebo were observed at weeks 8 and 24 for the 12-DU dose and at week 24 for the 6-DU dose (Fig 2, B, and Table II). The greatest effect on TOSSs was 67.9% relative to placebo (mean difference, -1.27 ; $P < .001$), which was observed at week 24 with the 12-DU dose.

A dose- and time-dependent effect of MK-8237 was observed for TSSs (Fig 2, C). Significant improvements in TSSs relative to placebo were observed at weeks 8, 16, and 24 for the 12-DU dose and at week 24 for the 6-DU dose (Fig 2, C, and Table II). The greatest effect on TSSs was 52.2% relative to placebo (mean difference, -4.84 ; $P < .001$), which was observed at week 24 with the 12-DU dose.

Exploratory assessments

For the total study population, asthma symptom scores were numerically lower at weeks 8, 16, and 24 in subjects receiving

both MK-8237 doses compared with those seen in subjects receiving placebo (see Fig E3, A, in this article's [Online Repository](#) at [www.jacionline.org](#)). These differences in asthma symptoms were more pronounced when only subjects with a reported history of asthma were analyzed (see Fig E3, B). No statistical analyses were conducted for asthma symptoms.

Prechallenge RQLQ(S)12+ scores from 6 DU- and 12 DU-treated subjects improved by 8% (mean difference, -0.21) and 11% (mean difference, -0.23), respectively, over the study period. A significant improvement in prechallenge RQLQ(S)12+ scores (26%) relative to placebo was observed at week 24 for the 12-DU dose (mean difference, -0.64 ; $P = .007$; see Fig E4, A, in this article's [Online Repository](#) at [www.jacionline.org](#)). No significant improvements in RQLQ(S)12+ scores were observed for the 6-DU dose at any time point. Prechallenge VAS symptom scores for the placebo- and 6 DU-treated subjects worsened 31% and 3%, respectively, over the study period, whereas the VAS score for 12 DU-treated subjects improved by 28%. A significant improvement in prechallenge VAS scores (-49%) relative to placebo was observed at week 24 for the 12-DU dose (mean difference, -18.41 ; $P = .001$; see Fig E4, B). No significant improvements in VAS scores were observed for the 6-DU dose at any time point. No significant improvement on change from prechallenge AAR were observed relative to placebo with either MK-8237 dose at any time point (data not shown).

Immunologic parameters

Specific IgE and IgG₄ levels increased with the 12-DU and 6-DU treatments versus placebo at week 8 based on the prespecified analyses ($P < .001$, Fig 4). *Post hoc* analyses on the subset of subjects ($n = 52$) with immunologic data available at week 24 showed sustained significant increments with IgE and IgG₄ levels at week 24 (see Fig E5 in this article's [Online Repository](#) at [www.jacionline.org](#)).

Safety

Both MK-8237 doses were well tolerated. There were no reported anaphylactic reactions or reactions requiring epinephrine, and there were no serious treatment-related AEs. The majority of treatment-related AEs were transient local allergic reactions of the mouth and throat (Table III). A few of the subjects experienced local allergic reactions, such as throat irritation and lip swelling, each day during the treatment period, although none of these subjects discontinued because of these reactions. Most AEs were assessed as mild or moderate in intensity. No local swelling in the mouth or throat was assessed as severe. A total of 9 subjects discontinued from the trial (12-DU dose, $n = 3$; placebo, $n = 6$); 1 discontinuation was due to vertigo, and the other 8 discontinuations were due to a decrease of 25% in peak expiratory flow or FEV₁ during chamber challenge sessions (a prespecified safety precaution). None of the AEs that led to study discontinuation were considered treatment related.

DISCUSSION

In this EEC study at the VCC, dose- and time-dependent improvements in nasal scores, ocular scores, and TSSs were observed with an HDM SLIT tablet (MK-8237) relative to

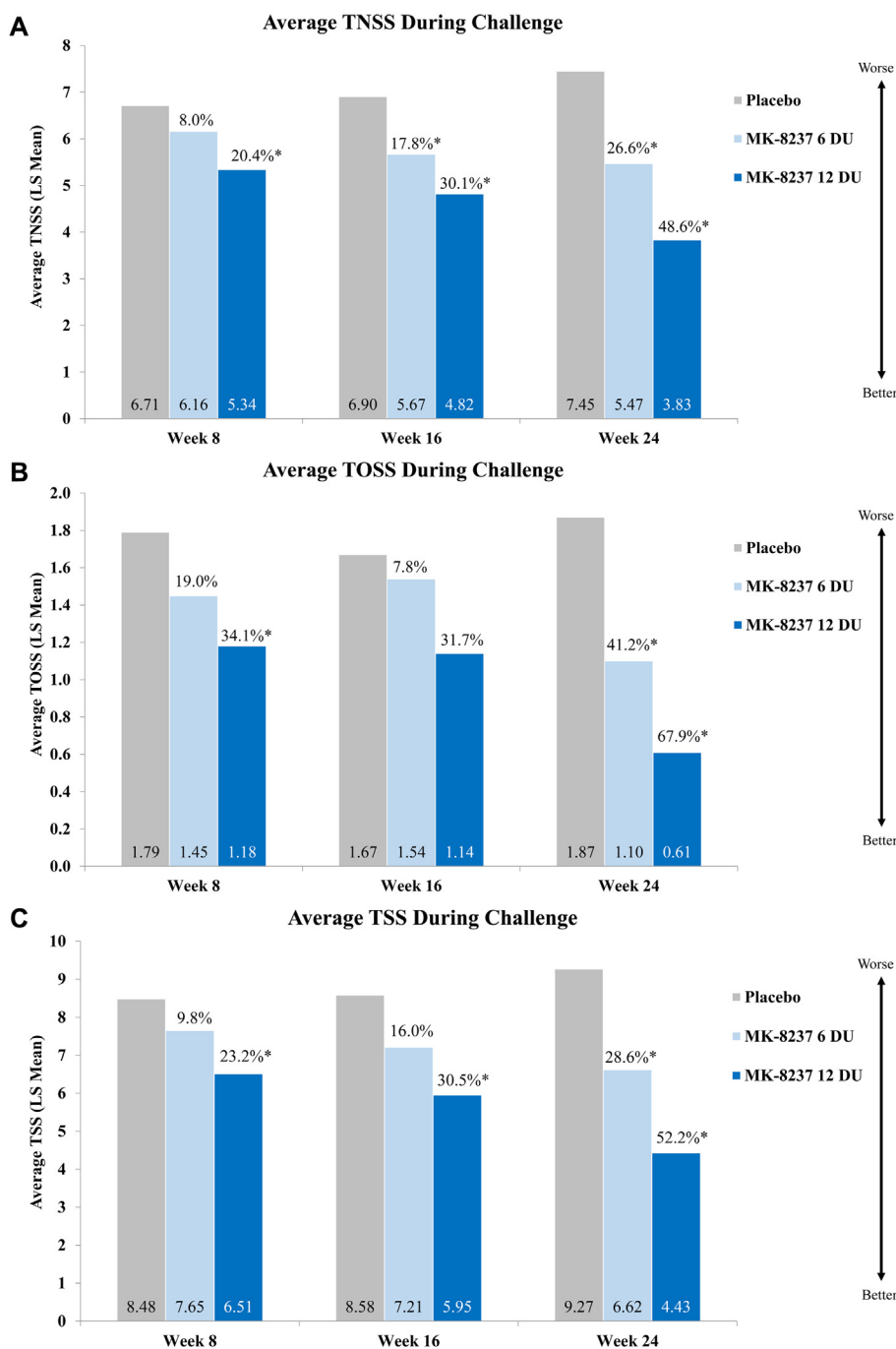


FIG 2. Total nasal symptom scores (A), ocular symptom scores (B), and nasal plus ocular symptom scores (C) at each study time point. Percentages represent the treatment difference relative to placebo. * $P < .05$ versus placebo. LS, Least square.

placebo. MK-8237, 12 DU, exhibited a greater effect versus placebo than the 6-DU dose. Efficacy of MK-8237 increased over time, with the greatest efficacy observed at the end of the study (week 24). Onset of action was dose dependent and began as early as week 8 (the earliest time point measured) for the 12-DU dose.

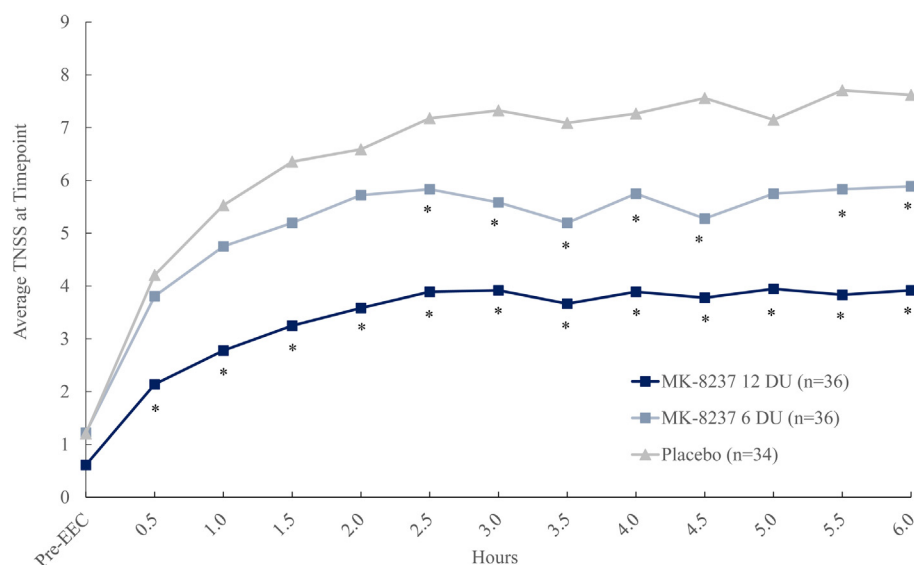
Although not directly comparable because it was a field study, Bergmann et al¹⁷ reported results on nasal and ocular symptoms from another randomized, double-blind, placebo-controlled HDM SLIT tablet trial. The study assessed the efficacy and safety of 2 doses of a different HDM SLIT tablet over 1 year in 509

subjects with moderate-to-severe HDM-induced AR.¹⁷ After 1 year of treatment, both active doses (300 and 500 IR) significantly improved the primary end point of average adjusted symptom score (a TSS adjusted for rescue medication use) by 17.9% and 20.2%, respectively, relative to placebo. In contrast to the current study, there did not appear to be a dose-dependent effect for efficacy. An EEC dose-finding study of 100-, 300-, and 500-IR HDM SLIT tablets demonstrated a dose-dependent effect in that only the higher 2 doses significantly changed the area under the curve from baseline in TSSs.¹⁸

TABLE II. Treatment difference from placebo for TNSSs, TOSSs, and TSSs

	MK-8237, 12 DU			MK-8237, 6 DU		
	Week 8	Week 16	Week 24	Week 8	Week 16	Week 24
Subjects, no.	40	39	36	39	36	36
TNSS						
Treatment difference	−1.37	−2.08	−3.62	−0.54	−1.23	−1.98
<i>P</i> value	.007	<.001	<.001	.198	.03	.003
Reduction vs placebo (% [95% CI])	−20.4 (−6.8 to −33.3)	−30.1 (−16.8 to −42.3)	−48.6 (−35.3 to −60.2)	−8.0 (4.0 to −19.3)	−17.8 (−2.6 to −31.1)	−26.6 (−11.2 to −39.6)
TOSS						
Treatment difference	−0.61	−0.53	−1.27	−0.34	−0.13	−0.77
<i>P</i> value	.02	.08	<.001	.235	.691	.02
Reduction vs placebo (% [95% CI])	−34.1 (−7.5 to −54.7)	−31.7 (3.7 to −58.1)	−67.9 (−41.2 to −87.4)	−19.0 (13.7 to −42.2)	−7.8 (37.3 to −38.0)	−41.2 (−9.9 to −62.7)
TSS						
Treatment difference	−1.97	−2.62	−4.84	−0.83	−1.37	−2.65
<i>P</i> value	.004	<.001	<.001	.18	.09	.003
Reduction vs placebo (% [95% CI])	−23.2 (−8.8 to −36.3)	−30.5 (−15.3 to −43.9)	−52.2 (−37.0 to −65.0)	−9.8 (4.8 to −22.3)	−16.0 (2.0 to −30.5)	−28.6 (−11.6 to −41.8)

For the primary end point, multiplicity was controlled by using a step-down procedure in which the comparison between 12 DU of MK-8237 and placebo was conducted first. Nominal *P* values were reported for secondary end points.

**FIG 3.** TNSSs over 6 hours during the chamber challenge session at week 24. **P* < .05 versus placebo.

HDM-induced AR is known to produce the classic nasal symptoms of AR, which was the justification for the primary end point assessment of TNSS. Less data are available regarding the prevalence of ocular symptoms in patients with HDM-induced AR, and there is a general perception that ocular symptoms are less frequent in patients with HDM allergy compared with patients allergic to seasonal allergens. The results of this study indicate that ocular symptoms were a prominent feature of the rhinoconjunctivitis syndrome, although it is possible that ocular symptoms might differ in a controlled challenge setting from those experienced as a result of in-field exposure. Nevertheless,

MK-8237 demonstrated a significant effect on both nasal and ocular symptoms in subjects with HDM-induced AR/C. In the HDM SLIT tablet field study that evaluated a different HDM SLIT tablet and was reported by Bergmann et al,¹⁷ only 1 ocular symptom (ocular itching) was assessed, and it was significantly improved by the 500-IR dose.

There is limited knowledge about the onset of action for HDM SLIT. In the current study the onset of action for the 12-DU dose was week 8, the earliest time point measured. This is in contrast to the field trial of an HDM SLIT tablet in which the onset of action was determined to be 4 months (earliest measured time point was

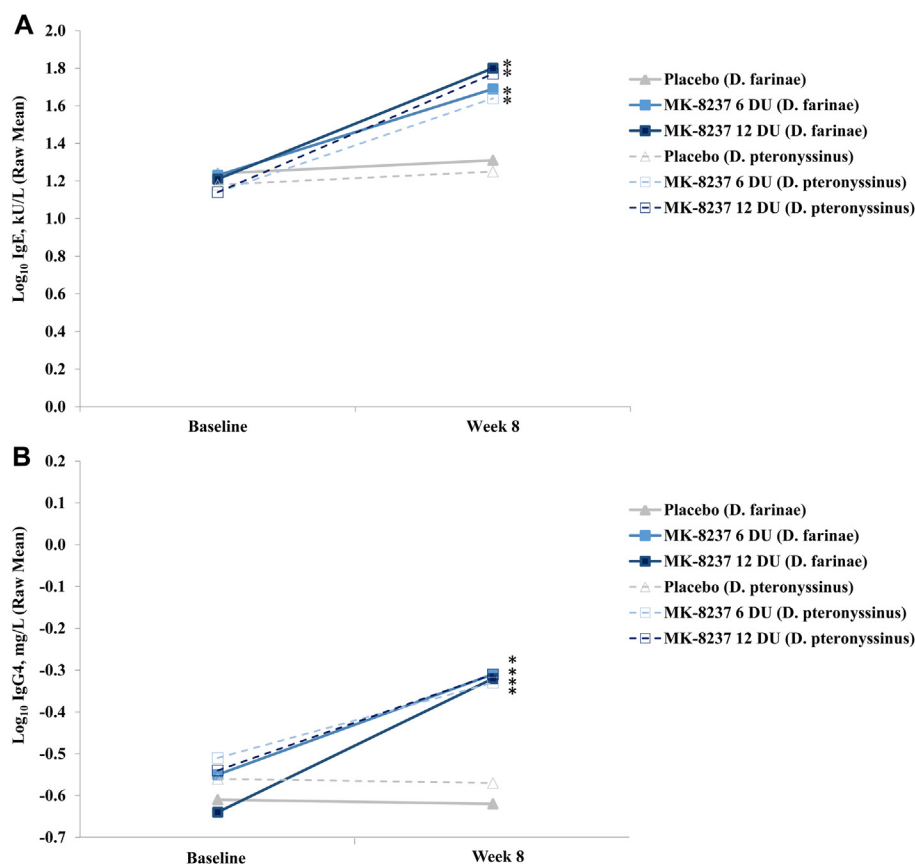


FIG 4. Log₁₀-transformed specific IgE (A) and IgG₄ (B) levels at screening and week 8. **P* < .001 versus placebo for least square means.

TABLE III. Treatment-related AEs

Treatment-related AEs	MK-8237, 12 DU (n = 42 [%])	MK-8237, 6 DU (n = 41 [%])	Placebo (n = 41 [%])
Subjects with any treatment-related AEs	76	61	5
Treatment-related AEs in ≥5% of subjects in ≥1 treatment group			
Throat irritation	52	34	0
Mouth edema	24	24	0
Lip swelling	17	5	2
Oral pruritus	14	15	0
Dyspepsia	10	2	0
Ear pruritus	7	0	0
Swollen tongue	5	0	0
Oropharyngeal swelling	5	0	0
Pharyngeal edema	5	2	0

2 months).¹⁷ One randomized, placebo-controlled field trial of 120 subjects using HDM sublingual drops assessed the onset of action as 14 weeks (earliest measured time point was 1 week).¹⁹ In another field trial of HDM sublingual drops in 108 elderly subjects, onset of action was not formally assessed, but clinical effect on nasal symptoms appeared to begin at approximately 6 months.²⁰ Thus, the onset of action of 12 DU of MK-8237 appears to be almost twice as fast as has been reported for HDM SLIT in other trials.

The immunologic data were supportive of the observed clinical effect, and it was of interest to note that the specific IgG₄ antibody levels continued to increase without reaching a plateau in the 12-DU treatment group. In addition, specific IgE and IgG₄ levels demonstrated a dose- and time-dependent change similar to the clinical end points.

There was a minimal response in the placebo group in the current trial (ie, placebo scores were nearly identical throughout the study). Subjects did not receive any special training and were only trained on how to score symptoms (ie, instructed not to score based on AR history). As previously suggested in other studies, a limitation of SLIT trials is bias introduced by compromised blinding from local reactions in subjects receiving active treatment, a possibility that cannot be ruled out for this study. However, the AE rate was similar for both active doses, and a consistent dose-dependent treatment effect across multiple end points suggests proper unbiased treatment group comparisons. In addition, recent ragweed SLIT tablet trials with prespecified sensitivity analysis of subjects with and without local AEs did not reveal any bias affecting the overall efficacy assessment.^{21,22}

A strong correlation between symptoms experienced during controlled exposure and in-field allergen exposure has been demonstrated,¹¹ although this correlation has yet to be demonstrated with HDM. However, an improvement from the prechallenge RQLQ(S)12+ and prechallenge VAS symptom scores reflecting the preceding weeks' symptoms was demonstrated for the 12-DU group. Although some AR studies propose the

minimally important difference (MID) for RQLQ score as a 0.5-point improvement from baseline²³ and this MID was not met for the longitudinal analyses, the cross-sectional analyses showed a −0.64 difference at week 24. However, using the MID to interpret the data is not as straightforward as it might appear. The MID for the RQLQ score has not been validated in perennial AR studies that use a similar design as the current study or for immunotherapy trials. Therefore the data must be interpreted with caution and preferably be supplemented with a number needed to treat analysis in future studies. With these methodological limitations, the RQLQ and VAS data still support a potentially clinically relevant treatment effect of 12 DU outside of the controlled HDM chamber exposure. Improvements in AAR results were not clearly observed because of wide SDs for these results across the 3 treatment groups. Furthermore, prechallenge values were not well balanced across the treatment groups at the different time points.

MK-8237 was generally well tolerated at both the 12 and 6 DU doses. The AEs reported in this study were similar to those reported in earlier trials of MK-8237.^{12,24} Most of the treatment-related AEs were transient local allergic reactions of mild-to-moderate severity, which is consistent with other SLIT products.⁵ There was little difference in the tolerability profiles of 6 and 12 DU of MK-8237.

Some of the strengths of this study are due to the controlled nature of EEC studies. For example, inherent limitations of in-field studies, such as variable allergen exposure among subjects, are not applicable. The trial was also designed to avoid challenge sessions during pollen seasons to minimize seasonal AR symptoms experienced by polysensitized subjects. The study duration was 6 months, which is in contrast to typically longer treatment regimens for immunotherapy; however, future field trials can address longer-term efficacy and magnitude of efficacy under variable environmental conditions.

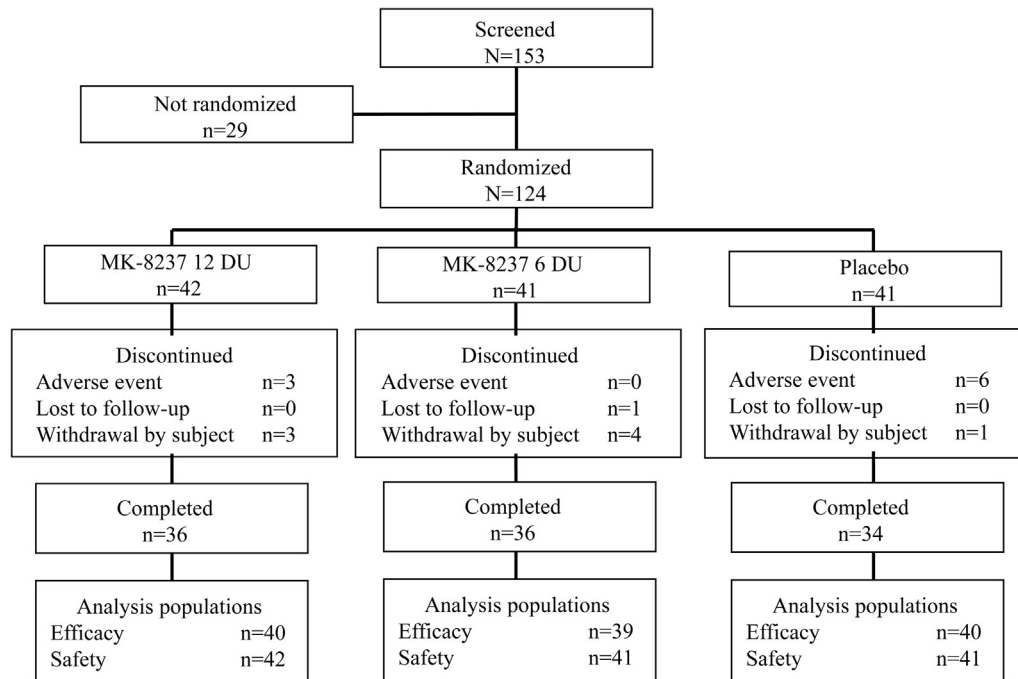
In conclusion, the efficacy and safety results indicate that the 12-DU dose of MK-8237 is appropriate for further evaluation in field trials for the treatment of HDM-induced AR/C with or without asthma based on its superior efficacy and similar safety profile compared with the 6-DU dose. The treatment effect of 12 DU of MK-8237 on both TNSS and TOSS was substantially greater than 20%, with an upper bound of the 95% CI of less than −10%, which is considered clinically meaningful according to the World Allergy Organization and US Food and Drug Administration.²⁵ Onset of action was as early as 8 weeks.

We thank Louise Broge and Christian Ljørring of ALK-Abelló, Hørsholm, Denmark, for reviewing the manuscript. Medical writing and editorial assistance was provided by Erin P. Scott, PhD, and assistance was funded by Merck & Co. Editorial assistance was also provided by Jorge Moreno-Cantu, PhD, Global Scientific and Medical Publications, Merck Research Laboratories, Merck & Co.

Clinical implications: Efficacy and safety results indicate that the 12-DU dose of the HDM SLIT tablet MK-8237 is appropriate for further evaluation in the treatment of HDM-induced allergic rhinoconjunctivitis.

REFERENCES

- Pichler CE, Marquardsen A, Sparholt S, Lowenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D. farinae* results in decreased bronchial hyperactivity. *Allergy* 1997;52:274-83.
- Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy* 2010;24:e104-9.
- Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol* 2013;31:233-41.
- Hsu NM, Reisacher WR. A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. *Int Forum Allergy Rhinol* 2012;2:280-4.
- Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6.
- Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol* 2013;132:1322-36.
- Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on "dose-response relationship in allergen-specific immunotherapy". *Allergy* 2011;66:1345-59.
- Durham SR, Nelson HS, Nolte H, Bernstein DI, Creticos PS, Li Z, et al. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. *Allergy* 2014;69:617-23.
- Devillier P, Le Gall M, Horak F. The allergen challenge chamber: a valuable tool for optimizing the clinical development of pollen immunotherapy. *Allergy* 2011;66:163-9.
- Ellis AK, North ML, Walker T, Steacy LM. Environmental exposure unit: a sensitive, specific, and reproducible methodology for allergen challenge. *Ann Allergy Asthma Immunol* 2013;111:323-8.
- Jacobs RL, Harper N, He W, Andrews CP, Rather CG, Ramirez DA, et al. Responses to ragweed pollen in a pollen challenge chamber versus seasonal exposure identify allergic rhinoconjunctivitis endotypes. *J Allergy Clin Immunol* 2012;130:122-7.e8.
- Corzo JL, Carrillo T, Pedemonte C, Plaza Martin AM, Martin Hurtado S, Dige E, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. *J Investig Allergol Clin Immunol* 2014;24:154-61.
- Arlian LG, Bernstein D, Bernstein IL, Friedman S, Grant A, Lieberman P, et al. Prevalence of dust mites in the homes of people with asthma living in eight different geographic areas of the United States. *J Allergy Clin Immunol* 1992;90:292-300.
- Tovey ER, Chapman MD, Platts-Mills TA. Mite faeces are a major source of house dust allergens. *Nature* 1981;289:592-3.
- Ziegelmayer P, Ziegelmayer R, Bareille P, Rousell V, Salmon E, Horak F. Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber. *Curr Med Res Opin* 2008;24:1833-40.
- Stubner P, Ziegelmayer R, Horak F. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit—the Vienna Challenge Chamber (VCC). *Curr Med Res Opin* 2004;20:891-902.
- Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133:1608-14.e6.
- Roux M, Yang WH, Viatte A, Cadic V, Abiteboul K, Zeldin RK, et al. Efficacy of house dust mite sublingual immunotherapy in adults with allergic rhinitis: results of an environmental exposure chamber study [abstract]. *J Allergy Clin Immunol* 2013;131:AB37.
- Wang DH, Chen L, Cheng L, Li KN, Yuan H, Lu JH, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope* 2013;123:1334-40.
- Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy* 2013;43:242-8.
- Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol* 2013;131:1342-9.e6.
- Nolte H, Hebert J, Berman G, Gawchik S, White M, Kaur A, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol* 2013;110:450-6.e4.
- Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;98:843-5.
- Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.e7.
- Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;62:317-24.

**FIG E1.** Subject disposition.

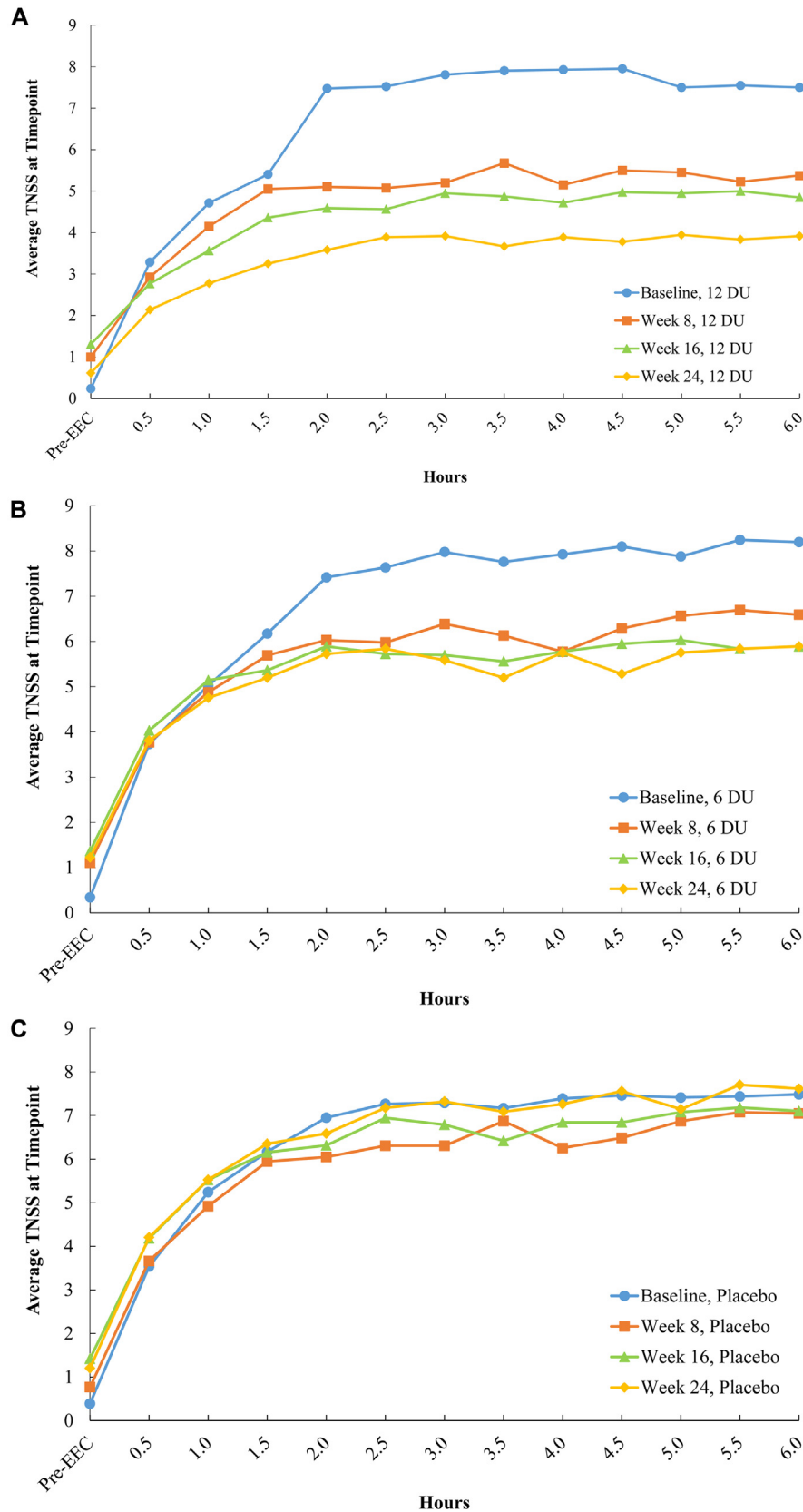


FIG E2. TNSSs over 6 hours during each chamber challenge session for 12 DU of MK-8237 (**A**), 6 DU of MK-8237 (**B**), and placebo (**C**).

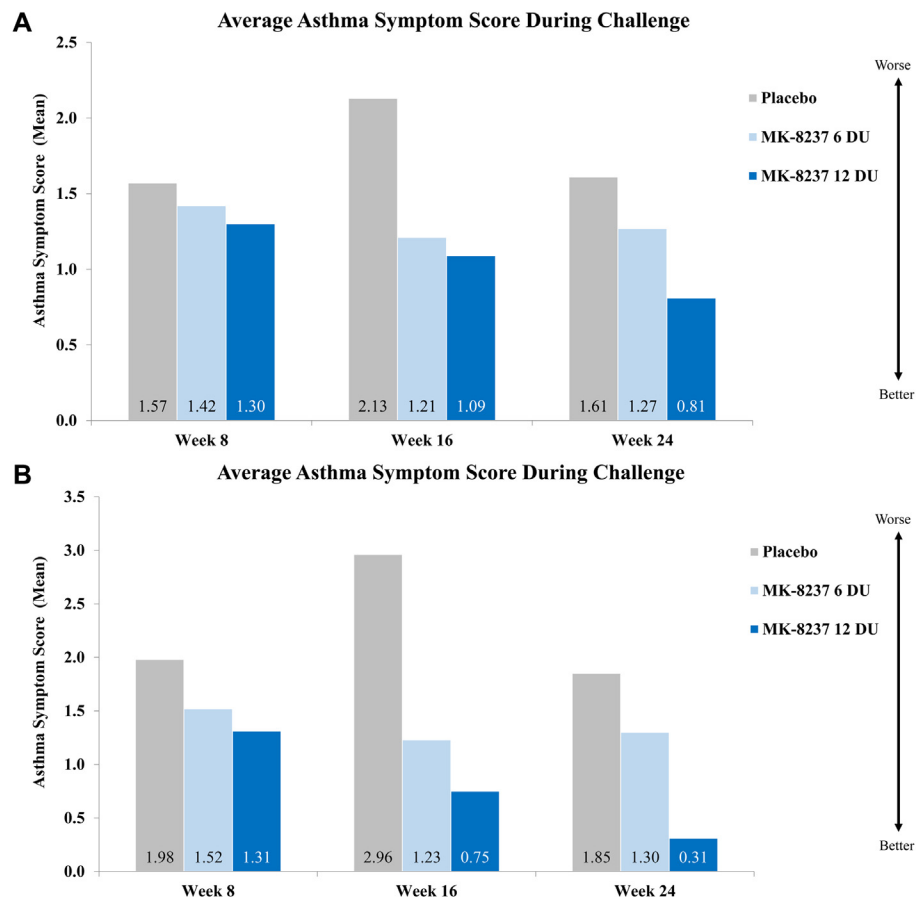


FIG E3. Asthma symptom scores at each study time point for the full analysis set (**A**) and subjects with asthma (**B**).

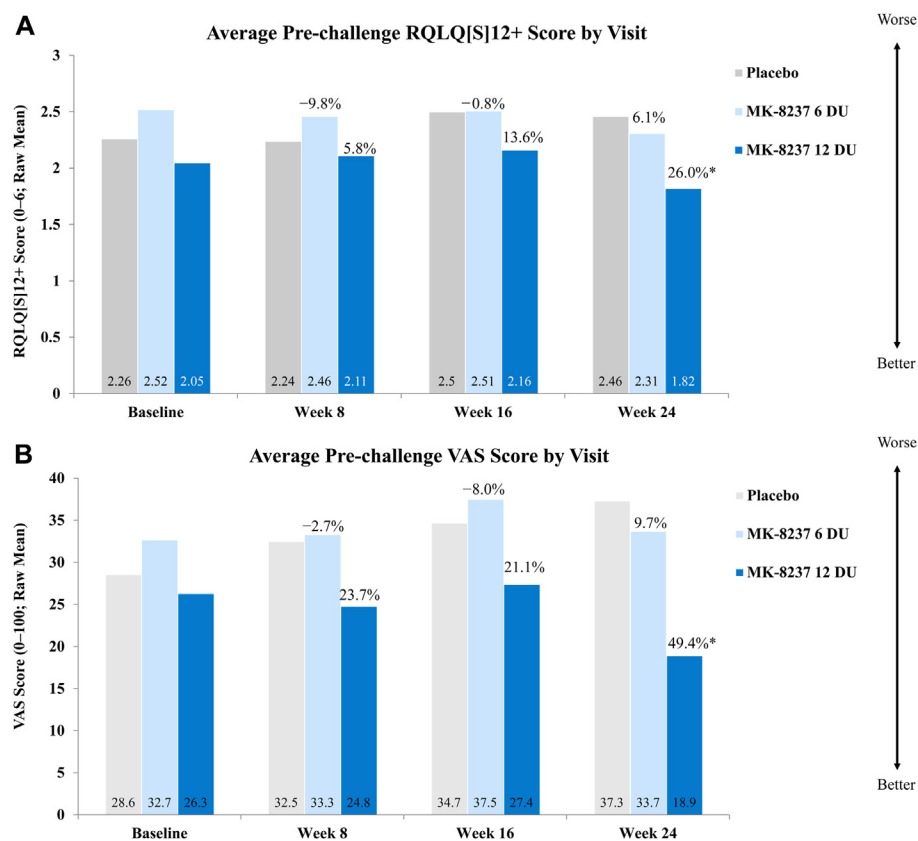


FIG E4. Prechallenge RQLQ(S)12+ scores (**A**) and rhinoconjunctivitis symptoms assessed based on VAS scores (**B**) from baseline to week 24. Percentages represent treatment differences relative to placebo for least square means. * $P < .05$ versus placebo for least square means. Percentage change from baseline for the RQLQ(S)12+ score was +9%, -8%, and -11% for the placebo-, 6 DU-, and 12 DU-treated groups, respectively. Percentage change from baseline for the VAS score was +31%, +3%, and -28% for the placebo-, 6 DU-, and 12 DU-treated groups, respectively.

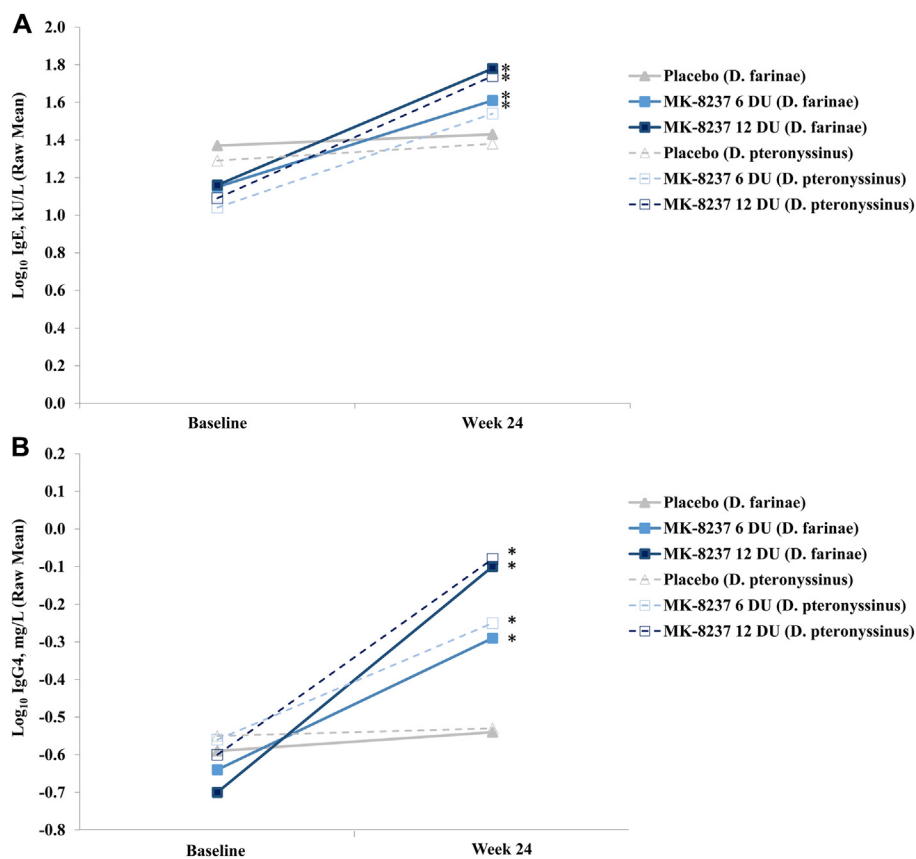


FIG E5. Log₁₀-transformed specific IgE (A) and IgG₄ (B) levels at screening and week 24 in a subset of subjects (n = 52). **P* < .001 versus placebo for least square means.

TABLE E1. Symptom scoring

Individual symptoms scored every 15 min during chamber challenge	Severity*	
	Score range	Maximum daily score [†]
Runny nose	0-3	3
Blocked nose	0-3	3
Sneezing	0-3	3
Itchy nose	0-3	3
TNSS		12
Gritty feeling/red/itchy eyes	0-3	3
Watery eyes	0-3	3
TOSS		6
TSS = TNSS + TOSS		18
Cough	0-3	3
Wheeze	0-3	3
Dyspnea	0-3	3
Total asthma symptom score		9

*Severity:

No symptoms = 0

Mild symptoms = 1

Moderate symptoms = 2

Severe symptoms = 3

[†]Average of symptom scores from the last 4 hours of the chamber challenge.