

Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial

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Background: The house dust mite (HDM) sublingual immunotherapy (SLIT) tablet (MK-8237; Merck & Co, Kenilworth, NJ/ALK-Abelló, Hørsholm, Denmark) has demonstrated beneficial effects on allergic rhinoconjunctivitis and asthma outcomes in European trials.

Objective: This is the first trial to assess the efficacy/safety of HDM SLIT-tablets in North American subjects with HDM-induced allergic rhinitis with or without conjunctivitis (AR/C). **Methods:** In this double-blind, multicenter trial (NCT01700192) 1482 subjects (aged ≥ 12 years) with HDM-induced AR/C with or without asthma were randomized to a daily SQ HDM SLIT-tablet (12 SQ-HDM dose) or placebo for up to approximately 52 weeks. A rhinitis daily symptom score (DSS; 4 nasal symptoms, maximum score = 12) of 6 or greater, or 5 or greater with 1 symptom being severe, on 5 of 7 consecutive days before randomization was required. The primary end point was the average total combined rhinitis score, which was defined as the rhinitis DSS plus rhinitis daily medication score (DMS), during the last 8 treatment weeks.

Results: Treatment with 12 SQ-HDM improved the total combined rhinitis score by 17% (95% CI, 10% to 25%) versus placebo. Improvements versus placebo in the secondary end

points of average rhinitis DSS, rhinitis DMS, total combined rhinoconjunctivitis score, and visual analog scale-assessed AR/C symptoms were 16%, 18%, 17%, and 16%, respectively. All nominal *P* values were less than .001 versus placebo, except rhinitis DMS (*P* = 0.15). No treatment-related adverse events meeting the International Council on Harmonization definition of a serious adverse event were reported; 1 nonserious treatment-related systemic allergic reaction occurred (assessed as moderate intensity) at first administration under medical supervision and was treated with epinephrine.

Conclusions: In the first North American trial of use of a SLIT-tablet for HDM allergy, 12 SQ-HDM was well tolerated and improved HDM-induced rhinitis symptoms in adults and adolescents. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: Allergen immunotherapy, allergic rhinoconjunctivitis, house dust mite, sublingual immunotherapy tablet, North America, adolescents

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House dust mite (HDM) is the most common cause of perennial allergic rhinitis with or without conjunctivitis (AR/C) worldwide. Symptoms of HDM-induced AR/C can be treated with allergy pharmacotherapy or allergy immunotherapy (AIT). In contrast to pharmacotherapy, AIT can alter the immune response to modify the underlying pathologic mechanisms of AR/C,¹ and sublingual immunotherapy (SLIT) tablets have shown long-lasting sustained efficacy for seasonal AR/C for 2 years after 3 years of treatment.²

HDM SLIT-tablets (MK-8237; Merck & Co, Kenilworth, NJ/ALK-Abelló, Hørsholm, Denmark) are manufactured by using a unique formulation (rapid dissolving on mucosal contact) and novel process that ensures a constant potency ratio of group 1 and group 2 major HDM allergens of the *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* mite species. The 12 SQ-HDM dose was demonstrated to be well tolerated in safety trials of subjects 5 years of age and older^{3,4} and significantly improved nasal and ocular symptoms in an environmental exposure chamber trial⁵ and in a randomized, double-blind, placebo-controlled (DBPC) European field trial.⁶ The SQ HDM SLIT-tablet has also demonstrated beneficial effects on asthma outcomes in European patients with HDM-induced allergic asthma.^{7,8} Subsequently, the SQ-HDM SLIT-tablet was approved in Europe in 2015 for the treatment of HDM-induced AR/C and allergic asthma.

Abbreviations used

AE:	Adverse event
AIT:	Allergy immunotherapy
AR/C:	Allergic rhinitis with or without conjunctivitis
DBPC:	Double-blind, placebo-controlled
DMS:	Daily medication score
DSS:	Daily symptom score
FAS:	Full analysis set
HDM:	House dust mite
ICS:	Inhaled corticosteroid
RQLQ(S)12+:	Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for Subjects ≥ 12 Years of Age
SLIT:	Sublingual immunotherapy
TCRS:	Total combined rhinitis score
TCS:	Total combined score
VAS:	Visual analog scale

According to a national survey, nearly one third of the US population is sensitized to HDM.⁹ However, the efficacy of subcutaneous or sublingual AIT for HDM-induced AR/C has not been conclusively demonstrated in North American patients. Only 1 randomized DBPC trial for HDM AIT has been conducted in the United States, and no significant effect on symptoms or medication use versus placebo was detected.¹⁰ The lack of effect might be attributable to the small size of the trial ($n = 31$) and relatively low exposure to environmental HDM allergens. The objective of this trial was to evaluate the efficacy and safety of the SQ HDM SLIT-tablet in North American subjects with HDM-induced AR/C.

METHODS**Trial design**

This randomized double-blind trial was conducted at 182 sites in the United States and Canada from January 2013 to April 2015 (P001; clinicaltrials.gov identifier NCT01700192). Subjects received daily SQ HDM SLIT-tablets (12 SQ-HDM dose) or placebo for up to approximately 52 weeks, preceded by a run-in phase of up to 6 weeks when subjects were not allowed to use antiallergy medications (see Fig E1 in this article's Online Repository at www.jacionline.org). Between March and August of 2014, subjects were randomized centrally by the investigator using an interactive voice or Web response system; randomization was stratified by asthma status (asthma/nonasthma) and age (<18 and ≥ 18 years). Blinding was maintained by use of identical packaging, appearance, smell, and taste of the SQ HDM SLIT-tablets and placebo; the sponsor, subjects, investigators, and trial personnel were blind to treatment. Compliance was monitored by means of subject interview during trial visits.

The trial was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. Institutional review boards approved the protocol, and written informed consent was obtained from the subject or the subject's legal representative.

Treatments

The SQ HDM SLIT-tablet is a fast-dissolving (<10 seconds) freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *D pteronyssinus* and *D farinae*. Source material containing extracted mite bodies, as well as mite feces, of *D pteronyssinus* and *D farinae* ensures that the tablet contains the broadest possible spectrum of *D pteronyssinus* and *D farinae* major and minor allergens. In addition, a highly standardized production process ensures a 1:1:1:1 potency ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2. The 12 SQ-HDM dose contains roughly 15 μ g of group 1 mite

allergens (Der f 1 and Der p 1 combined) and 15 μ g of group 2 mite allergens (Der f 2 and Der p 2 combined).¹¹

First administration of treatment occurred at the trial site, followed by a 30-minute observation under medical supervision. Subsequent doses were self-administered at home. Open-label symptom-relieving medications were provided before the 8-week efficacy assessment period, and subjects were instructed to obtain permission from the trial site before their first use. A total symptom score of 4 or greater or persistent eye symptoms was required before permission was given. Self-injectable epinephrine was provided at randomization in the event of an anaphylactic reaction, and subjects were instructed on its use.

Key inclusion and exclusion criteria

Eligible subjects were 12 years of age or older, with a history of 1 year's duration or more of HDM-induced AR/C that required treatment during the previous year. Subjects with adequately controlled asthma ($FEV_1 \geq 80\%$ of predicted value at screening and randomization) that required, at most, a daily medium dose of an inhaled corticosteroid (ICS) were allowed in the trial. A positive skin prick test response (wheal diameter ≥ 5 mm greater than that induced by the saline control) to *D pteronyssinus* or *D farinae* (10,000 AU/mL, ALK-Abelló) and a specific IgE level of 0.7 kU_A/L or greater against *D pteronyssinus* or *D farinae* at screening were required. Subjects were also required to have a rhinitis daily symptom score (DSS) of 6 or greater, or 5 or greater with 1 symptom being severe, on 5 of 7 consecutive days before becoming eligible for randomization; a washout period for antiallergy medications was required before and during the run-in period until the rhinitis symptom threshold was met.

Patients with unstable or severe asthma, as judged by the investigator, were excluded from the trial, as were those sensitized and regularly exposed to non-HDM perennial allergens during the run-in and efficacy assessment periods; those with a history of symptomatic seasonal AR/C to an allergen to which the subject is sensitized and regularly exposed, which potentially overlapped with the run-in and efficacy assessment periods; those with any nasal condition that could confound the efficacy or safety assessments; those with a history of anaphylaxis with cardiorespiratory symptoms with prior AIT of an unknown cause or because of an inhalant allergen; those receiving a high-dose ICS for asthma within 6 months before screening; and those with an occurrence of clinical deterioration of asthma that resulted in emergency treatment, hospitalization, or systemic corticosteroid treatment in the 3-month period before the screening and run-in periods.

Assessments

The efficacy assessment period was approximately the last 8 weeks of treatment and was timed to occur when HDM exposure per physician judgment was expected to be at its peak with little interference from pollen allergens. Across the trial, the 8-week efficacy assessment period ranged from September to April depending on the location, so as not to overlap with pollen seasons. The primary end point was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. The TCRS was the sum of the rhinitis DSS and rhinitis daily medication score (DMS). The rhinitis DSS was the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) scored on a scale of 0 (none) to 3 (severe). The rhinitis DMS was calculated based on daily use of symptom-relieving medications for nasal symptoms (see Table E1 in this article's Online Repository at www.jacionline.org). Subjects scored symptoms daily in an electronic diary during the run-in period, and scored symptoms and recorded symptom-relieving medication use daily during the efficacy assessment period.

Secondary end points were the average rhinitis DSS, rhinitis DMS, total combined score (TCS; sum of rhinoconjunctivitis DSS and rhinoconjunctivitis DMS; see Table E1), and AR/C symptoms assessed by using a visual analog scale (VAS; scale = 0-100) during the last 8 weeks of treatment. Exploratory end points included the average asthma DSS (sum of cough, wheezing, and chest tightness/dyspnea symptoms scored on a scale of 0-3) and the average Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for Subjects ≥ 12 Years of Age (RQLQ[S]12+) during the last 8 weeks

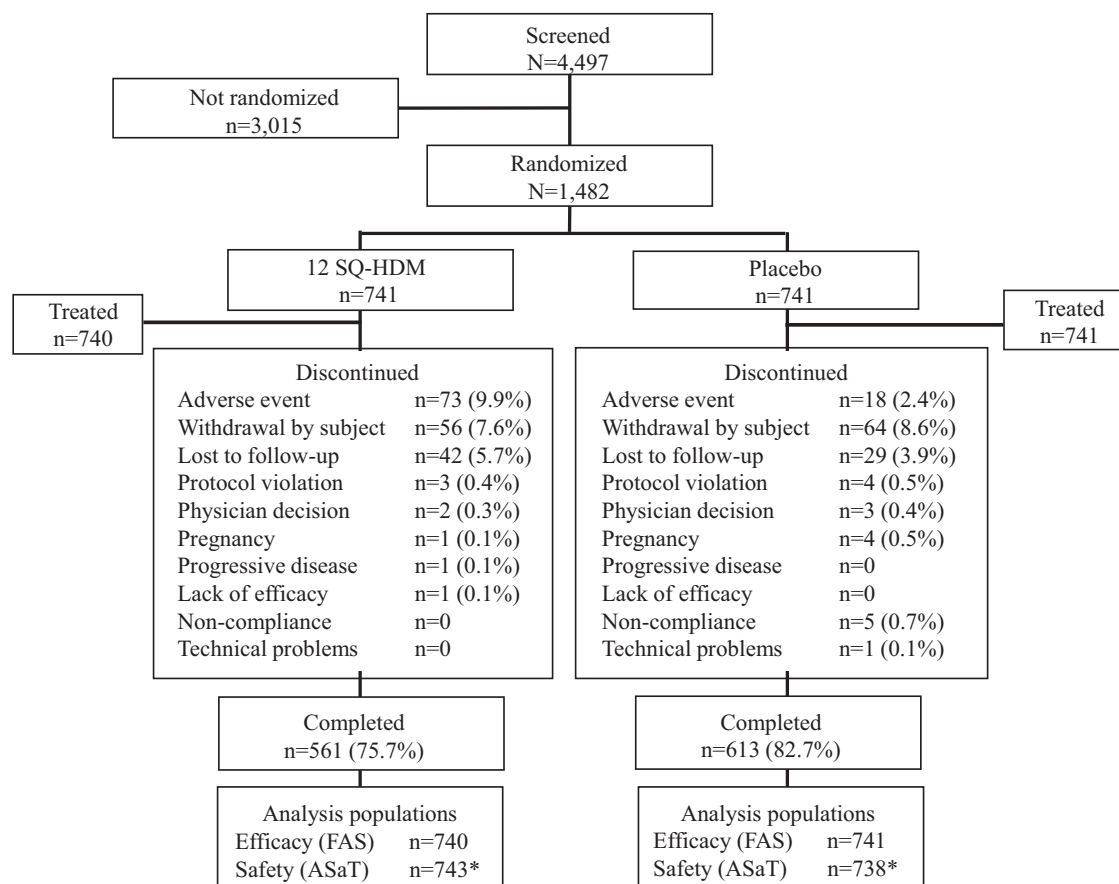


FIG 1. Subject disposition. *Five subjects were cross-treated; 3 subjects were randomized to placebo and received 1 or more doses of 12 SQ-HDM, and 2 subjects were randomized to 12 SQ-HDM and received 1 or more doses of placebo. ASaT, All subjects as treated.

of treatment. Serum was collected at run-in, week 4, week 20, and the final week of treatment for analysis of HDM-specific IgE and IgG₄ levels.

Investigators interviewed subjects during trial visits regarding the presence of adverse events (AEs). Safety was also assessed by soliciting local AEs using a side effect report card developed by the sponsor and completed by subjects daily for the first approximately 28 days of treatment. Subjects completed the side effect report card based on symptoms that occurred within 60 minutes of dosing. By using closed-ended questions, the side effect report card captured local AEs identified by the World Allergy Organization as being associated with SLIT.¹² The intensity and relatedness to AE treatment were determined by investigators. Information on time to onset, duration in minutes, and recurrence was collected for prespecified local AEs. There were 2 events of accidental overdose with subsequent development of mild AEs (oral pain, oral pruritus, and throat irritation).

Statistical analysis

For sample size calculations, assuming a 14% dropout rate, a total of 750 subjects per group were randomized so that approximately 645 subjects per group were eligible for the efficacy assessment period. With approximately 645 subjects per group and a true difference in medians of -1.66 in the primary end point between the 12 SQ-HDM and placebo groups, the trial had greater than 99% power for the primary analysis at a significance α level of 0.05 (2-sided). In addition, there was approximately 85% power to have the upper bound of the 95% CI for the percentage difference in 12 SQ-HDM relative to placebo of less than -10% , assuming a median TCRS of 7.54 for subjects in the placebo group.

The primary analysis was conducted on the full analysis set (FAS), which considered all subjects who received 1 or more doses of study treatment.

Within the FAS population, subjects with insufficient efficacy data (ie, subjects with no E-diary data during the efficacy assessment period) did not contribute to efficacy analyses. Insufficient efficacy data were due to early dropout before the start of the efficacy assessment period. The safety analysis was conducted on the "All subjects as treated" population, which included all subjects who received 1 or more doses of study treatment, according to the treatment actually received. Baseline values were calculated based on data collected during the last 7 consecutive days before subjects met the rhinitis symptom score eligibility criteria. The primary end point was analyzed by using a prespecified nonparametric approach in which between-treatment comparison was performed with the Wilcoxon rank sum test. The Hodges-Lehmann estimate of treatment difference and the corresponding 2-sided 95% CIs were also reported. Treatment difference relative to placebo was calculated as follows:

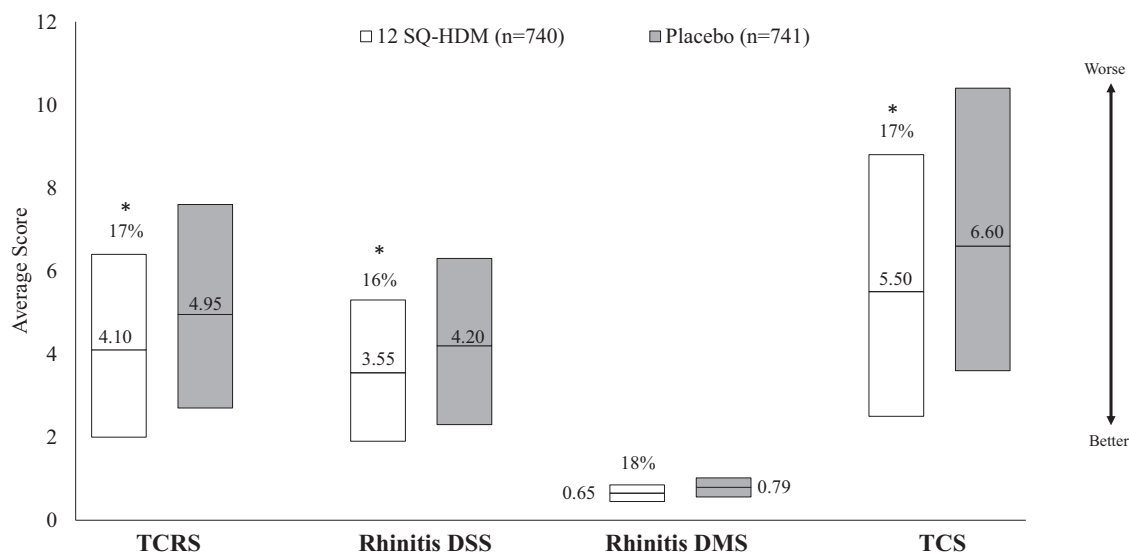
$$100\% \times (12 \text{ SQ-HDM} - \text{placebo}) / \text{Placebo}$$

based on medians (or means for rhinitis DMS); the 95% CI was based on the bootstrap method using 10,000 iterations. Key secondary end points were analyzed in the following order for purposes of multiplicity control: rhinitis DSS, rhinitis DMS, TCS, and VAS AR/C score using the same method as the primary end point, except for rhinitis DMS. For analysis of rhinitis DMS, the zero-inflated log-normal model was used (with treatment, baseline asthma status, age group, and region as fixed effects) because more than 30% of the rhinitis DMS values were zero. Ninety-five percent CIs were calculated by using the Δ method. The primary and key secondary end points were tested in a stepwise manner to control for type I error under multiple hypotheses. Statistical analyses were conducted with SAS software (version 9.4; SAS Institute, Cary, NC).

TABLE I. Baseline characteristics and demographics (randomized subjects)

	12 SQ-HDM (n = 741)	Placebo (n = 741)
Women, no. (%)	445 (60)	430 (58)
Age (y), mean $\pm$ SD (range)	35 $\pm$ 14 (12-77)	35 $\pm$ 14 (12-85)
White, no. (%)	567 (77)	564 (76)
Asthmatic patients, no. (%)	228 (31)	232 (31)
ICS use, no. (%) [*]	66 (29)	62 (27)
FEV ₁ (% predicted), mean $\pm$ SD [*]	98.3 $\pm$ 16.7	97.2 $\pm$ 11.1
Duration of AR/C (y), mean $\pm$ SD	18 $\pm$ 13	19 $\pm$ 13
IgE sensitization type, no. (%)		
HDM only	184 (25)	171 (23)
HDM and other allergens	555 (75)	567 (77)
Not sensitized to HDM [†]	2 (0.3)	3 (0.4)
<i>D farinae</i> SPT wheal size (mm), mean $\pm$ SD	10.9 $\pm$ 4.4	11.1 $\pm$ 4.4
<i>D pteronyssinus</i> SPT wheal size (mm), mean $\pm$ SD	11.1 $\pm$ 4.5	11.3 $\pm$ 4.3
<i>D farinae</i> serum specific IgE (kU/L), mean $\pm$ SD	14.1 $\pm$ 20.7	16.0 $\pm$ 21.5
<i>D pteronyssinus</i> serum specific IgE (kU/L), mean $\pm$ SD	13.7 $\pm$ 20.8	14.5 $\pm$ 20.4

SPT, Skin prick test.

^{*}Of asthmatic patients.[†]Protocol violators.**FIG 2.** Efficacy outcome scores during approximately the last 8 weeks of treatment (full analysis set). Plots are medians (upper/lower quartiles) except for rhinitis DMSs, which are estimated means (95% CIs). Percentages indicate improvement in scores relative to placebo. *Nominal *P* values of less than .001 versus placebo. *TCS*, Total combined rhinoconjunctivitis symptom and medication score.

RESULTS

Subjects

A total of 1482 subjects were randomized; all but 1 received treatment for a median duration of 271 days, and 79% of subjects completed the trial (Fig 1). Demographics and baseline characteristics were similar between the 2 treatment groups (Table I). Nearly one third of the subjects (31%) had a history of asthma, 28% of whom reported ICS use at baseline. In addition to reporting perennial AR/C, 68% had a history of seasonal AR/C symptoms, and 65% reported perennial conjunctivitis. Most subjects (76%) were polysensitized to allergens other than HDM.

Efficacy

Overall mean compliance with study drug was 96%. During the efficacy assessment period, there was a significantly lower

average TCRS with 12 SQ-HDM versus placebo ($P < .001$, Fig 2), with a treatment difference based on medians corresponding to an improvement of 17% (95% CI, 10% to 25%; Table II). In a subgroup analysis of HDM-monosensitized and polysensitized subjects, the average TCRS improved 17% and 18%, respectively. Similarly, in a subgroup of 32% subjects reporting perennial AR/C without seasonal AR/C symptoms, the average TCRS improved 18%. The average rhinitis DSS was significantly lower with 12 SQ-HDM versus placebo ($P < .001$, Fig 2), corresponding to an improvement of 16% (95% CI, 7% to 24%) based on median scores. Conjunctivitis symptom scores were also lower with 12 SQ-HDM treatment, with an improvement versus placebo of 33% (95% CI, 19% to 47%). By the end of the trial, the majority of subjects had not used any symptom-relieving medications; 57% of subjects had an average rhinitis DMS of zero. The average rhinitis DMS was not significantly different with 12 SQ-HDM

TABLE II. Treatment difference in average TCRS during approximately the last 8 weeks of treatment with SQ HDM SLIT-tablet versus placebo (full analysis set)

Treatment	Baseline TCRS, mean (SD)	Average TCRS during the last 8 wk of treatment, median (lower-upper quartiles)
12 SQ-HDM (n = 566)	7.94 (1.72)	4.10 (2.00 to 6.40)
Placebo (n = 620)	7.94 (1.76)	4.95 (2.70 to 7.55)
Hodges-Lehmann estimate of shift (95% CI)		−0.80 (−1.20 to −0.40)*
Improvement from placebo (% [95% CI])		17 (10 to 25)

* $P < .001$.

versus placebo ($P = .15$, Fig 2), although an improvement of 18% (95% CI, −4% to 41%) was observed. The improvements in average TCS and AR/C VAS scores with 12 SQ-HDM versus placebo were 17% (95% CI, 4% to 25%; Fig 2) and 16% (95% CI, 8% to 23%), respectively. The nominal P values for the average TCS and average AR/C VAS scores were less than .001 for 12 SQ-HDM versus placebo; however, because of the prespecified multiplicity control strategy, these results cannot be considered confirmatory.

In the FAS population least-square mean asthma DSS was 1.26 (baseline, 2.95) with 12 SQ-HDM and 1.56 (baseline, 3.12) with placebo during the efficacy assessment period, corresponding to a 19% improvement versus placebo ($P = .002$ for between-treatment difference). In a *post hoc* analysis of subjects with reported asthma, the least-square mean asthma DSS was 1.37 with 12 SQ-HDM (baseline, 3.45) and 1.83 with placebo (baseline, 3.86), for a difference of −0.46 (95% CI, −0.83 to −0.10), corresponding to a 25% improvement versus placebo. Least-square mean RQLQ(S)12+ scores were 1.56 (baseline, 2.64) with 12 SQ-HDM treatment and 1.84 (baseline, 2.66) with placebo during the efficacy assessment period, corresponding to a 0.28-point improvement versus placebo ($P < .001$ for between-treatment difference).

Immunologic parameters

Compared with baseline, treatment with 12 SQ-HDM resulted in an increase in HDM-specific IgE levels followed by a slight decrease over time (Fig 3). Similarly, IgG₄ levels increased over time (Fig 3).

Safety

Treatment with 12 SQ-HDM was well tolerated in the entire trial population and in subjects with a reported history of asthma. The incidence of treatment-emergent AEs was 91% with active treatment and 73% with placebo. The incidence of treatment-related AEs was 84% with active treatment and 41% with placebo, the most common of which were throat irritation, oral pruritus, and ear pruritus (Table III). Most treatment-related AEs were assessed as mild or moderate in intensity. The median onset of prespecified local allergic reactions ranged from 1 to 8 days (Table IV). The median duration (in minutes) of prespecified local allergic reactions on day 1 with active treatment varied from 14 to 67 minutes (Table V). In general, the sensation of swelling

persisted longer than the sensation of itch or irritation. The median recurrence of all prespecified local allergic reactions was 1 day (Table IV), indicating that events typically do not recur and are transient in nature.

In all, 7 subjects were treated with epinephrine because of AEs; 3 subjects received epinephrine for events related to 12 SQ-HDM. No treatment-related serious AEs were reported. One nonserious systemic allergic reaction related to 12 SQ-HDM was reported. The event, assessed by the investigator as moderate in intensity (AE verbatim terms: systemic reaction, facial flushing, itchy palms, and swollen throat), occurred within minutes of tablet administration on the first day of treatment under medical supervision and was treated with epinephrine by the investigator. This subject discontinued treatment.

In a second subject 1 event of local swelling (throat tightness) related to 12 SQ-HDM treatment was assessed as severe in intensity. The event occurred on day 7 of treatment within 30 minutes of tablet administration. The subject self-administered epinephrine and was subsequently treated in the emergency department. Prior reported events in this subject included itching in the mouth, throat irritation, and tongue pain on days 1 and 2 of trial drug administration. The subject discontinued the trial.

A third subject self-administered epinephrine in response to development of moderate throat and chest discomfort within 30 minutes of 12 SQ-HDM administration on day 128. The subject continued the trial and tolerated subsequent treatments.

There were 4 other epinephrine administrations during the trial unrelated to 12 SQ-HDM; 3 for food/environmental allergies and 1 in a placebo-treated subject with a complex constellation of allergy symptoms. The AEs of asthma, irrespective of causality, were reported in a similar percentage of subjects in the 12 SQ-HDM and placebo groups (1.3% vs 2.4%, respectively). The majority of these asthma events were mild or moderate in severity. No asthma events met the criteria for seriousness.

DISCUSSION

This was the largest randomized DBPC AIT trial for HDM-induced AR/C conducted to date and the first successful randomized DBPC trial for HDM AIT in North America. The results demonstrated a significant improvement with 12 SQ HDM SLIT-tablet treatment versus placebo for the TCRS, as well as the rhinitis DSS. A parallel improvement in AR/C VAS score provided supportive evidence for the beneficial effects of 12 SQ-HDM on symptoms. Furthermore, 31% of the subjects had a history of asthma, and 12 SQ-HDM improved asthma symptoms versus placebo.

Treatment with 12 SQ-HDM resulted in a 17% improvement in TCRS relative to placebo. Although not directly comparable, it is lower than the 49% improvement in symptoms observed with 12 SQ-HDM in a recently conducted HDM environmental exposure chamber trial.⁵ This improvement is also lower than the 20% improvement relative to placebo that is considered clinically relevant by the World Allergy Organization¹³ and the magnitude of effect observed with pollen SLIT-tablets in field trials.¹⁴⁻¹⁶ The current trial was powered to meet the US Food and Drug Administration's criteria for clinically meaningful efficacy. The US Food and Drug Administration criteria are a point estimate of the treatment difference relative to placebo of at least 15%, with a lower bound of the 95% CI of at least 10%.¹⁷ The results of the current

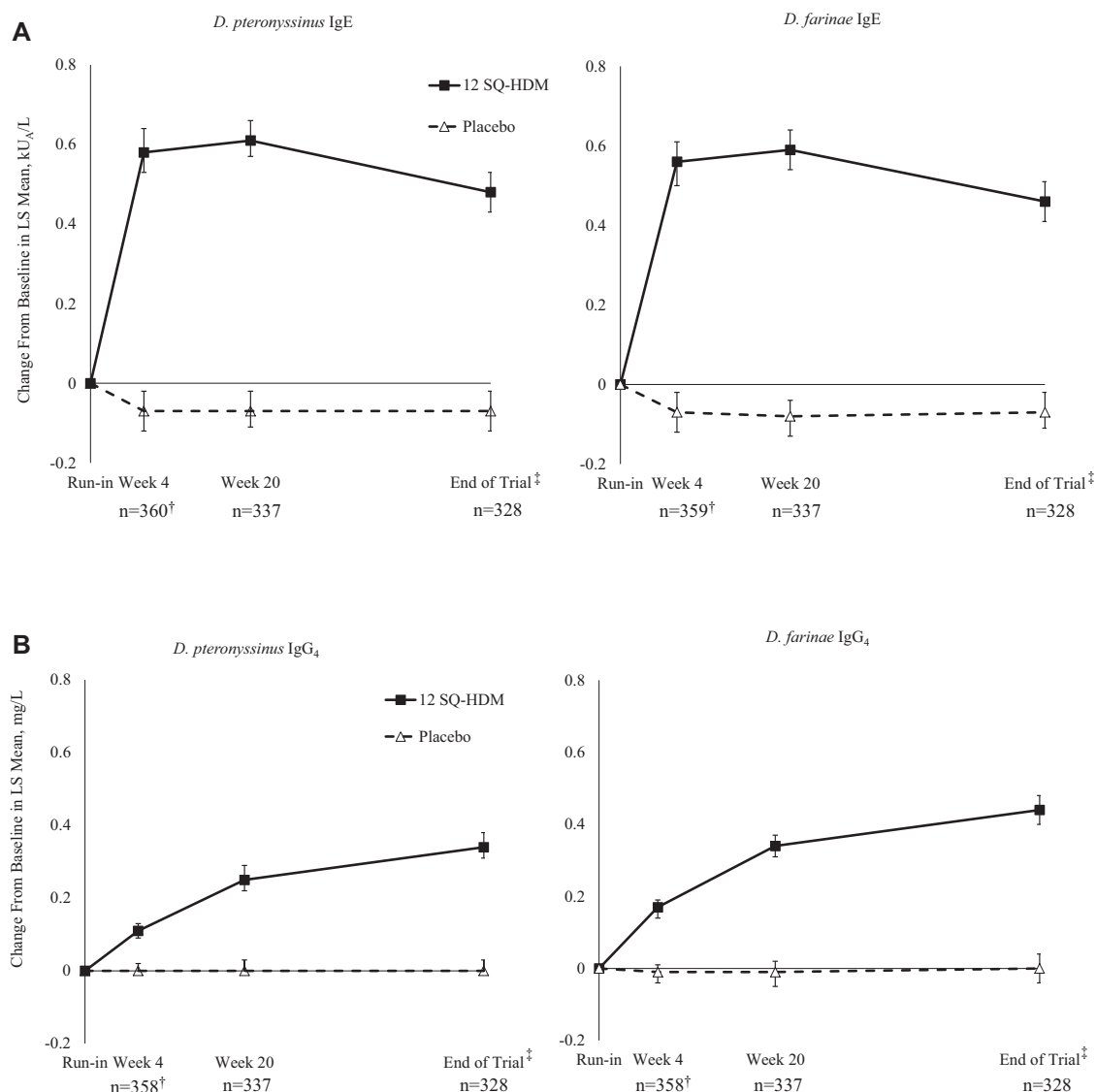


FIG 3. Change from baseline in immunologic parameters (log₁₀ scale) for IgE (**A**) and IgG₄ (**B**) by trial visit (full analysis set). Error bars indicate 95% CIs. [†]Only 400 subjects were selected to have immunologic samples analyzed. [‡]End of trial ranged from 35 weeks to 52 weeks from randomization. LS, Least square.

TABLE III. Treatment-related AEs reported by 10% or more of subjects in either treatment group (all subjects as treated)

Treatment-related AEs	12 SQ-HDM (n = 743 [% of subjects])	Placebo (n = 738 [% of subjects])
Throat irritation	67	22
Oral pruritus	62	14
Ear pruritus	51	11
Lip swelling	18	2
Glossodynia	15	3
Swollen tongue	16	2
Pharyngeal edema	14	3
Nausea	13	5
Tongue ulceration	13	2
Upper abdominal pain	11	4
Palatal swelling	11	1
Mouth ulceration	10	3

trial indicate these criteria were met. Furthermore, the World Allergy Organization recommendations selected 20% as the cutoff for minimal clinically relevant efficacy based on the opinion that the efficacy of an AIT product should not be inferior to that of antihistamines.¹³ In the meta-analysis by Wilson et al,¹⁸ the relative treatment effect of antihistamines was 7%. Later, in 2 independent meta-analyses that examined the effect of antihistamines relative to a “true” placebo for seasonal AR/C, the overall weighted mean relative improvement in rhinitis DSS was 12%¹⁹ and 15%.²⁰ Thus neither the TCRS (which includes the symptom-reducing effects of antihistamines and intranasal steroids) nor the rhinitis DSS with 12 SQ-HDM in the current trial were inferior to a historical antihistamine effect, which suggests the effect observed with the HDM SLIT-tablet was clinically relevant. In addition, the current trial results were similar to European in-field study results with 12 SQ-HDM reported by Demoly et al⁶ and might represent a more realistic magnitude of effect to be

TABLE IV. Median day of onset and recurrence for prespecified local AEs (all subjects as treated)

AE	12 SQ-HDM (n = 743)	Placebo (n = 738)
Throat irritation, no.	506	172
Median onset (d [range])	1 (1-223)	2 (1-134)
Median recurrence (d [range])	1 (1-370)	1 (1-280)
Oral pruritus, no.	468	109
Median onset (d [range])	1 (1-85)	2 (1-225)
Median recurrence (d [range])	1 (1-374)	1 (1-280)
Ear pruritus, no.	382	92
Median onset (d [range])	1 (1-30)	5 (1-190)
Median recurrence (d [range])	1 (1-375)	1 (1-313)
Lip swelling/edema, no.	151	19
Median onset (d [range])	5 (1-207)	3 (1-164)
Median recurrence (d [range])	1 (1-374)	1 (1-144)
Swollen tongue/edema, no.	133	17
Median onset (d [range])	8 (1-189)	3 (1-22)
Median recurrence (d [range])	1 (1-60)	1 (1-26)
Pharyngeal edema/throat tightness, no.	113	24
Median onset (d [range])	3 (1-272)	6 (1-29)
Median recurrence (d [range])	1 (1-209)	1 (1-33)
Palatal swelling/edema, no.	89	11
Median onset (d [range])	3 (1-51)	4 (1-22)
Median recurrence (d [range])	1 (1-29)	1 (1-4)
Mouth swelling/edema, no.	75	12
Median onset (d [range])	8 (1-152)	4 (1-206)
Median recurrence (d [range])	1 (1-310)	1 (1-58)
Tongue pruritus, no.	36	7
Median onset (d [range])	2 (1-110)	1 (1-2)
Median recurrence (d [range])	1 (1-225)	1 (1-17)
Oropharyngeal swelling/edema, no.	1	0
Median onset (d [range])	1 (1-1)	—
Median recurrence (d [range])	1 (1-1)	—

expected in AIT in-field trials of perennial AR/C. Interestingly, the efficacy of some antiallergy medications might be less for perennial AR/C than seasonal AR/C,²¹ and patients with perennial AR/C tend to be less satisfied with their treatment compared to patients with seasonal AR/C.^{22,23}

A limitation of the current field trial was that there was no measurement of HDM exposure or steps to control exposure. Individual subject HDM exposure caused by variability by season, use of air conditioning, mattress/pillow covers, carpet removal, and other environmental differences could have interfered with the trial results.²⁴ Furthermore, a notable decrease in symptom scores in the placebo group from baseline to the end of the trial was observed. The lower symptom scores might be related to the use of symptom-relieving medication use, which was not allowed during the baseline period, or lower HDM exposure. Other possibilities are that a “regression toward the mean” or a “Hawthorne effect” with altered behavior on observation²⁵ resulted in lower scores at the end of the trial because subjects were required to be highly symptomatic at baseline. However, the 49% improvement in rhinitis DSS relative to placebo with 12 SQ-HDM in the environmental chamber challenge trial suggests a very effective immunotherapy formulation.⁵

12 SQ-HDM was well tolerated, with a safety profile characteristic of SLIT-tablets for seasonal AR/C.^{16,26} Although local AEs were frequent, they were considered tolerable because of the mild intensity of the AEs, as well as the short duration and

TABLE V. Median duration in minutes of prespecified local AEs after dosing on day 1 (all subjects as treated)

AE	12 SQ-HDM (n = 743)	Placebo (n = 738)
Throat irritation, no.	393	85
Median duration (min [range])	31 (1-785)	45 (1-810)
Oral pruritus, no.	329	50
Median duration (min [range])	30 (1-796)	60 (1-1149)
Ear pruritus, no.	272	29
Median duration (min [range])	30 (1-624)	90 (5-600)
Lip swelling/edema, no.	34	4
Median duration (min [range])	60 (10-864)	15 (15-15)
Swollen tongue/edema, no.	25	6
Median duration (min [range])	30 (2-120)	10 (10-10)
Pharyngeal edema/throat tightness, no.	44	7
Median duration (min [range])	30 (3-240)	381 (10-850)
Palatal swelling/edema, no.	36	2
Median duration (min [range])	34 (10-360)	87 (60-113)
Mouth swelling/edema, no.	12	3
Median duration (min [range])	35 (10-240)	10 (2-10)
Tongue pruritus, no.	17	6
Median duration (min [range])	14 (3-25)	25 (15-30)
Oropharyngeal swelling/edema, no.	1	0
Median duration (min [range])	67 (67-67)	—

For AEs that were reported to last more than 1 day or reoccurred after day 1 of dosing, the duration of the event was imputed to 1380 minutes. For reporting purposes, the duration of an event was capped by the smaller value of the duration from first dose to the end of the day and the largest reported duration that was less than 1380 minutes for the same AE within the same treatment group.

recurrence of these events. The discontinuation rate caused by AEs was similar to that in previous reports of SLIT-tablet treatment.^{6,14,15,27} In contrast to previous SLIT-tablet trials in which AEs were reported spontaneously, this trial actively solicited local AEs from subjects daily on a report card for the first approximately 28 days. The solicitation of AEs likely explains the high proportion of local AEs because the placebo group in the current trial reported AE rates similar to rates observed in subjects on SLIT-tablet treatment in trials that used spontaneous AE reporting.^{6,16,27} The incidence of mouth/tongue ulceration was higher than in the pivotal North American timothy grass and ragweed SLIT-tablet trials,^{14,15,27-29} but a cognitive debriefing study suggested that subjects might have misinterpreted the question (“Have you experienced mouth ulcer/sore in the mouth?” Or “Have you experienced tongue ulcer/sore on the tongue?”) as mouth/tongue pain rather than an actual ulcer.

Only 1 randomized DBPC AIT trial for HDM had been conducted previously in the United States, and no significant improvement in symptoms was detected.¹⁰ Many other trials have also failed to demonstrate a significant effect on symptoms with HDM AIT. Indeed, of the 26 randomized DBPC SLIT and subcutaneous immunotherapy trials for HDM-induced AR/C published through March 2014, as identified in 2 systematic reviews,^{30,31} only 10 reported a significant effect on AR/C symptoms.^{4,32-40} The lack of efficacy in many of these trials might have been due to inadequate HDM extract formulations, inadequate numbers of subjects, use of subtherapeutic doses, or individual variations in allergen exposure. In contrast, the current trial contributes to the accumulated evidence supporting the efficacy and safety of SLIT-tablets for perennial and seasonal AR/C.^{5,6,14,15,27-29,41,42}

In the first North American trial of a SLIT-tablet for HDM allergy, 12 SQ-HDM was effective and well tolerated in North

American adolescent and adult subjects with HDM allergy, most of whom were polysensitized. The trial confirms results from previous European trials, which indicate that once-daily SQ HDM SLIT-tablet is well tolerated and effective.

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Clinical implications: The once-daily SQ HDM SLIT-tablet can be used to effectively treat HDM allergy in North American adults and adolescents. Treatment was well tolerated.

REFERENCES

- Matsuoka T, Shamji MH, Durham SR. Allergen immunotherapy and tolerance. *Allergol Int* 2013;62:403-13.
- Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-25.e5.
- 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.
- Maloney J, Prenner BM, Bernstein DI, Lu S, Gawchik S, Berman G, et al. Safety of house dust mite sublingual immunotherapy standardized quality tablet in children allergic to house dust mites. *Ann Allergy Asthma Immunol* 2016;116:59-65.
- Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol* 2015;135:1494-501.e6.
- Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ-HDM SLIT-tablet: results from a randomized double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016;137:444-51.
- 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.
- Virchow JC, Backer V, Kuna P, Prieto L, Villesen HH, Ljorring C, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. *JAMA* 2016;315:1715-25.
- 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;116:377-83.
- Bush RK, Swenson C, Fahlberg B, Evans MD, Esch R, Morris M, et al. House dust mite sublingual immunotherapy: results of a US trial. *J Allergy Clin Immunol* 2011;127:974-81, e1-7.
- Henmar H, Frisette SMT, Grosch K, Nielsen K, Smith G, Sonderkaer S, et al. Fractionation of source materials leads to high reproducibility of SQ-HDM SLIT-tablets. *Int Arch Allergy Immunol* 2016;169:23-32.
- Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. *J Allergy Clin Immunol* 2013;132:93-8.
- 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.
- 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.
- Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80.e2.
- Nolte H, Amar N, Bernstein DI, Lanier BQ, Creticos P, Berman G, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol* 2014;113:93-100.e3.
- Allergic Products Advisory Committee (APAC) meeting, December 12, 2013. US Food and Drug Administration: 2013.
- Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116:338-44.
- Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol* 2011;128:791-9.e6.
- Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med* 2014;12:71.
- Durham SR, Creticos PS, Nelson HS, Li Z, Kaur A, Meltzer EO, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: pooled analyses. *J Allergy Clin Immunol* July 14, 2016 [E-pub ahead of print].
- Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. *Clin Otolaryngol Allied Sci* 2000;25:551-7.
- Rodrigo GJ, Neffen H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy* 2011;41:160-70.
- Pfaar O, Gerth van Wijk R. Mite-allergic rhinitis: how to evaluate clinical efficacy in allergen-specific immunotherapy trials? *Curr Treat Options Allergy* 2015;2:1-9.
- Cook DL. The Hawthorne effect in educational research. *Phi Delta Kappan* 1962;44:116-22.
- Nelson HS. Oral/sublingual *Phleum pratense* grass tablet (Grazax/Grastek) to treat allergic rhinitis in the USA. *Expert Rev Clin Immunol* 2014;10:1437-51.
- Maloney J, Bernstein DI, Nelson H, Creticos P, Hebert J, Noonan M, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol* 2014;112:146-53.e2.
- Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.e4.
- 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.
- 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.
- Nelson HS. Update on house dust mite immunotherapy: are more studies needed? *Curr Opin Allergy Clin Immunol* 2014;14:542-8.
- Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006;61:849-54.
- Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59:491-7.
- 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.
- 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.
- 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.
- 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 hyperreactivity. *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.
- Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351:629-32.
- Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73.e7.
- Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.

Online Repository

Table E1. Scoring of symptoms and medication use.

Symptom	Score	Maximum Daily Score	
Rhinitis DSS			
Runny nose	0=none	3	
Stuffy nose	1=mild	3	
Sneezing	2=moderate	3	
Itchy nose	3=severe	3	
Maximum rhinitis DSS		12	
Conjunctivitis DSS			
Itchy eyes	0=none	3	
Watery eyes	1=mild	3	
	2=moderate	3	
	3=severe	3	
Maximum conjunctivitis DSS		6	
Symptom-relieving Medication	Subject Dosing Instructions	Score/Dose Unit	Maximum Daily Score
Rhinitis DMS			
Loratadine tablet, 10 mg	1 tablet daily	4	4
Mometasone nasal spray, 50 µg/spray	2 sprays in each nostril daily	2	8
Maximum rhinitis DMS			12
Conjunctivitis DMS			

Loratadine tablet, 10 mg	1 tablet daily	2	2
Olopatadine hydrochloride, 0.1%	1 drop per eye, twice daily	1.5	6
Maximum conjunctivitis DMS			8
Maximum TCRS*			24
Maximum TCS[†]			38

DMS, daily medication score; DSS, daily symptom score; TCS, total combined score; TCRS, total combined rhinitis score.

*Sum of rhinitis DSS and rhinitis DMS.

[†]Sum of rhinoconjunctivitis DSS (rhinitis DSS+conjunctivitis DSS) and rhinoconjunctivitis DMS (rhinitis DMS+conjunctivitis DMS).

Online Repository Figure Legends

Figure E1. Trial diagram. HDM, house dust mite.

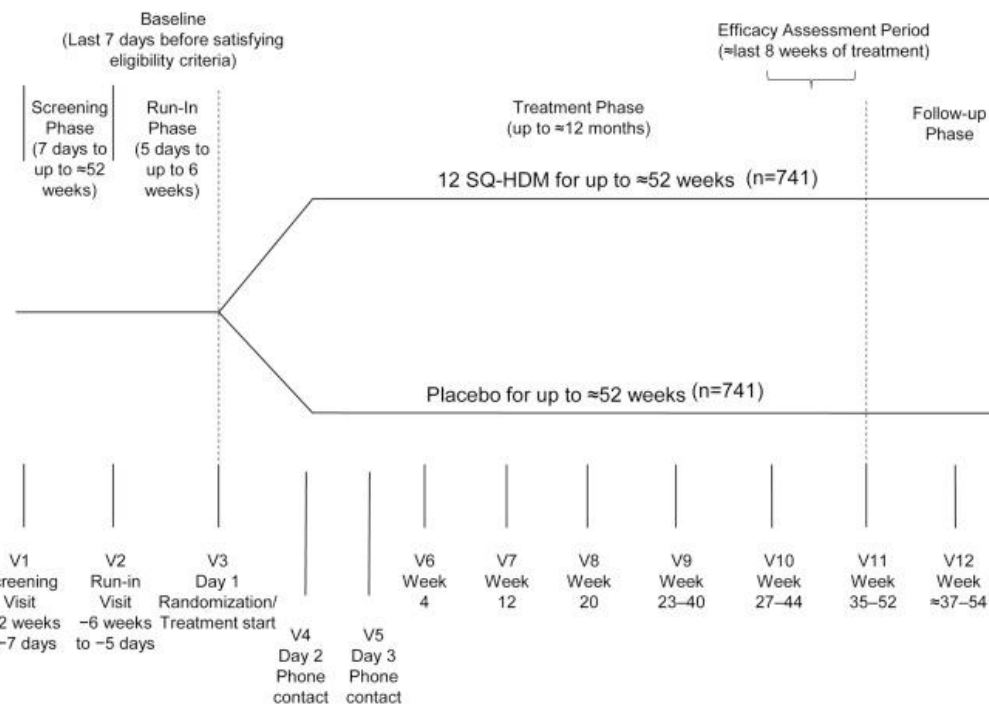


Fig E1.

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