

Long-term effects of a house dust mite sublingual immunotherapy tablet in an environmental exposure chamber trial

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ABSTRACT

Background: Treatment with SQ house dust mite (HDM) sublingual immunotherapy (SLIT) tablet is effective for HDM respiratory allergic disease, but data on long-term effects are lacking.

Objective: Post hoc analyses were conducted to determine the long-term effect of SQ HDM SLIT-tablet on nasal, ocular, and cough symptoms 1 year after discontinuation of treatment.

Methods: Study participants underwent environmental exposure chamber (EEC) challenges at baseline and week 24 in a randomized, placebo-controlled, double-blind trial (NCT01644617) during which participants received daily 12 SQ-HDM, 6 SQ-HDM, or placebo for 24 weeks. Asthma had to be stable, well controlled, and nonsevere. The mean total asthma symptom score (TASS; sum of 3 symptoms: cough, wheeze, and dyspnea) during baseline and week 24 EEC challenge was analyzed in all participants who completed the trial (n = 106). Approximately 1 year after trial completion, another EEC challenge was conducted in a subset of participants (n = 51). Total nasal symptom score (sum of 4 symptoms), total ocular symptom score (sum of 2 symptoms), and cough were assessed. **Results:** Compared with baseline and end-of-treatment values, sustained improvement of all symptoms assessed at the 1-year follow-up EEC challenge was evident in participants treated with 12 SQ-HDM. Results with 6 SQ-HDM were less notable. After 24 weeks of 12 SQ-HDM, TASS during EEC challenge was improved 65% vs baseline; at 1-year follow-up, cough was improved 57% vs baseline.

Conclusion: Persistent improvement of nasal and ocular symptoms was observed up to 1 year after completing 24 weeks of 12 SQ-HDM treatment. Beneficial effects on cough were also observed.

Trial Registration: clinicaltrials.gov Identifier NCT01644617.

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Introduction

House dust mite (HDM) is an important indoor allergen, with a sensitization prevalence of approximately 22% in Europe and 28% to 44% across North America.^{1–3} Clinical trials have found that treatment with a SQ HDM sublingual immunotherapy (SLIT) tablet (MK-8237; Merck & Co Inc, Kenilworth, NJ, and ALK, Hørsholm, Denmark) effectively reduces symptoms associated with HDM allergic rhinitis with or without conjunctivitis (AR/C).^{4–7} Evidence exists for a sustained treatment effect with grass SLIT tablets 2 years after a 3-year treatment period,^{8,9} and theoretically, HDM SLIT tablet treatment should also result in sustained improvement after treatment discontinuation because of the induction of immunologic tolerance and downregulation of effector cell mechanisms.¹⁰ Indeed, a different HDM SLIT tablet formulation caused a significant improvement in the primary efficacy measure up to 8

months after a 1-year treatment period, although this significance was not sustained at 12 months after treatment.¹¹ For the SQ HDM SLIT-tablet formulation, evidence supporting a long-term treatment effect is lacking.

Patients with allergic rhinitis to HDMs often have concomitant asthma, and there is a recognized pathophysiologic link between the 2 conditions.^{12,13} Presumably because of this link, in addition to demonstrated benefits for AR/C, the SQ HDM SLIT-tablet reduces the dose of inhaled corticosteroids (ICSs) in patients with HDM AR/C and asthma¹⁴ and reduces the risk of an asthma exacerbation in patients with HDM asthma not well controlled by ICSs.¹⁵

Environmental exposure chambers (EECs) are useful tools to evaluate the efficacy of treatments for AR/C.¹⁶ Within these chambers, individuals are exposed to controlled amounts of allergen that should induce noticeable symptoms in those with documented AR/C to the given allergen. Therefore, the ability of a treatment to limit symptoms is more easily detected during EEC challenges compared with environmental trials, where symptom severity may be low because of low or variable levels of allergen exposure and other confounding factors, such as concomitant medication. In a recently reported EEC trial, the efficacy and onset of action of 24 weeks of treatment with SQ HDM SLIT-tablet on rhinoconjunctivitis symptoms were demonstrated.⁵ The objective of this post hoc analysis was to evaluate the potential long-term effect of the SQ HDM SLIT-tablet on AR/C nasal and ocular symptoms during an EEC challenge conducted approximately 1 year after completion of the aforementioned EEC trial. Given the link between HDM AR/C and asthma, an additional objective was to explore the short- and long-term effect of the SQ HDM SLIT-tablet on asthma symptoms and cough during EEC challenge.

Methods

Study Design

Details of this randomized, placebo-controlled, double-blind, single-site trial (Vienna Challenge Chamber, Vienna, Austria) have been previously published (protocol P003; clinicaltrials.gov Identifier NCT01644617).⁵ Briefly, adults with a history of HDM-induced AR/C with or without a history of asthma were randomized 1:1:1 to daily 12 SQ-HDM, 6 SQ-HDM, or matching placebo for approximately 24 weeks. The EEC challenges at screening and weeks 8, 16, and 24 were timed to occur outside the regional tree and grass pollen seasons. A subset of the original trial population participated in an EEC challenge conducted approximately 1 year after trial completion as part of the Vienna Challenge Chamber's annual diagnosis update of allergic individuals. Each challenge session lasted 6 hours. The chamber itself is a 54-m³ sealed room in which a precisely defined and monitored (by weight) airborne concentration of HDM allergen (approximately 0.3 g of material per hour) was administered to individuals continuously and maintained.

The study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from participants before the study, and the protocol was approved by an independent ethics committee. The annual follow-up evaluation was also approved by an independent ethics committee.

Treatment

The SQ HDM SLIT-tablet is a fast-dissolving, freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *Dermatophagoides pteronyssinus* and *Dermatophagoides 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. A highly standardized

production process ensures a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2. The 12 SQ-HDM SLIT tablet contains approximately 15 µg of group 1 mite allergens (Der f 1 and Der p 1 combined) and 15 µg of group 2 mite allergens (Der f 2 and Der p 2 combined).¹⁷

Antihistamines and decongestants were not allowed for 3 days before randomization and before each exposure challenge (including the 1-year follow-up challenge), and bronchodilator use was not permitted on the day of any exposure challenges. The use of oral, nasal, or ocular corticosteroids was not permitted at any time during the trial. Low-dose inhaled corticosteroids were permitted.

Key Inclusion and Exclusion Criteria

Adults (≥18 years old) with HDM AR/C of 1 year or longer, with or without a history of asthma, were included. Only those with a forced expiratory volume in 1 second (FEV₁) of 70% predicted or higher were randomized; asthma had to be stable, well controlled, and nonsevere as judged by the investigator. Adults with asthma who required medium- or high-dose ICSs within the last 12 months before screening were excluded. A total nasal symptom score (TNSS; sum of runny nose, blocked nose, sneezing, and itchy nose; maximum score, 12) of 6 or higher within the first 2 hours of the screening (pretreatment) exposure challenge, a positive skin prick test result (wheal diameter ≥3 mm larger than saline control) to *D pteronyssinus* and/or *D farinae* at screening, and a positive serum specific IgE test result (≥0.7 kU/L equivalent to radioallergosorbent test class 2) to *D pteronyssinus* and/or *D farinae* at screening were required for inclusion.

One-Year Follow-up Inclusion

As part of the Vienna Challenge Chamber's annual diagnosis update of allergic individuals, all study participants were invited approximately 1 year (range, 9–12 months) after trial completion. Nevertheless, participation in the follow-up was optional at this time point.

Study Assessments

During the exposure challenges, symptoms were scored on a scale of 0 (none) to 3 (severe) every 15 minutes and recorded into an electronic database. The TNSS (sum of runny nose, blocked nose, sneezing, and itchy nose; maximum score, 12), total ocular symptom score (TOSS; sum of red/itchy eyes and watery eyes; maximum score, 6), and total asthma symptom score (TASS; sum of cough, wheeze, and dyspnea; maximum score, 9) were assessed from hours 0 to 6 throughout the EEC challenges. Mean TNSS, TOSS, TASS, and cough scores were calculated from hours 2 to 6 of the exposure challenges. At the 1-year follow-up visit, assessed symptoms were the same as in the original trial except cough was the only asthma symptom assessed. Wheeze and dyspnea were not assessed at follow-up because their assessment is not standard practice for the annual diagnosis update.

Asthma-related safety was monitored by spirometry and asthma control determined per investigator assessment. Spirometry was conducted within 30 minutes before each EEC challenge (prechallenge) and at the end of each challenge. Peak expiratory flow (PEF) was measured before challenge and approximately every 30 minutes during each challenge. Participation was to be terminated during the study for the following reasons: 1) a significant decrease in FEV₁ during an exposure challenge session (defined as FEV₁ of 20% below the prechallenge FEV₁), (2) a significant decrease in PEF during an exposure challenge session (defined as PEF of 25% below the prechallenge PEF), or (3) a late-phase asthmatic reaction requiring treatment intervention, temporally associated with an exposure chamber challenge, and determination by an investigator that continuation in the trial would be detrimental to the patient.

Statistical Analysis

The mean TASS for the baseline and week 24 exposure challenge was analyzed post hoc in all participants who completed the trial. Means of week 24 and 1-year follow-up TNSS, TOSS, and cough scores were calculated post hoc. Medians and quartiles were also calculated as a supplement to the mean and SD calculations. Baseline values were based on scores at the screening challenge. The percentage treatment difference relative to baseline was calculated as follows: (treatment–baseline)/baseline $\times$ 100%.

Results

Study Participants

A total of 124 participants were randomized in the trial (placebo, $n = 41$; 6 SQ-HDM, $n = 41$; 12 SQ-HDM, $n = 42$), and 106 participants completed the trial (placebo, $n = 34$; 6 SQ-HDM, $n = 36$; 12 SQ-HDM, $n = 36$). Participant disposition, baseline demographics, and clinical characteristics have been previously described.⁵ Of the randomized participants, 30 (24%) had a medical history of asthma, and 6 (5%) were using ICSs at baseline.

One-Year Follow-Up Nasal and Ocular Assessments

Of the 106 participants who completed the trial, compared with baseline values, mean TNSSs at week 24 improved 51%, 31%, and 0% with 12 SQ-HDM, 6 SQ-HDM, and placebo, respectively. In the same population, compared with baseline values, mean TOSSs at week 24 improved 72%, 50%, and 11% with 12 SQ-HDM, 6 SQ-HDM, and placebo, respectively.

Of the 106 participants who completed the trial, 51 had follow-up EEC challenge visits approximately 1 year later (placebo, $n = 16$; 6 SQ-HDM, $n = 19$; 12 SQ-HDM, $n = 16$). Of these follow-up participants, 24% had a medical history of asthma. In this subgroup of 51 follow-up participants, compared with baseline values, mean TNSSs at week 24 improved 47% and 30% with 12 SQ-HDM and 6 SQ-HDM, respectively, and worsened 11% with placebo; at the 1-year follow-up, improvements were 32% and 10% with 12

SQ-HDM and 6 SQ-HDM, respectively, and 10% with placebo (Fig 1). The TNSS during the 1-year follow-up exposure challenge was markedly improved with 12 SQ-HDM vs baseline (Fig 2). In this same group of follow-up participants, compared with baseline values, mean TOSSs at week 24 improved 63%, 39%, and 17% with 12 SQ-HDM, 6 SQ-HDM, and placebo, respectively; at the 1-year follow-up, improvements were 29%, 16%, and 18% with 12 SQ-HDM, 6 SQ-HDM, and placebo, respectively (Fig 3). The TOSS during the 1-year follow-up exposure was improved with 12 SQ-HDM vs baseline (Fig 4).

Asthma Symptoms

The proportion of participants in the total trial population with any asthma symptom (score >0) was similar at baseline among the treatment groups (approximately 90%) but decreased to 50% in the 12 SQ-HDM group, 69% in the 6 SQ-HDM group, and 82% in the placebo group at the week 24 challenge. For the 106 participants who completed the trial, the mean TASSs during week 24 exposure challenge in the 12 SQ-HDM group was improved 65% vs baseline and in the 6 SQ-HDM group was improved 53% vs baseline (Fig 5).

One-Year Follow-Up Cough Assessment

Wheeze and dyspnea were not measured at the 1-year follow-up challenge; therefore, a mean TASS could not be calculated. However, cough was a measured asthma symptom at the 1-year follow-up. Compared with baseline, cough at week 24 improved 63% and 55% with 12 SQ-HDM and 6 SQ-HDM, respectively, and worsened 6% with placebo; at 1-year follow-up, cough improved 57% with 12 SQ-HDM and worsened 10% and 60% with 6 SQ-HDM and placebo, respectively (Fig 6).

Asthma-Related Safety

Treatment was overall well tolerated, and participants with asthma tolerated the HDM SLIT tablet. No adverse events requiring epinephrine occurred. There was a slightly higher proportion of

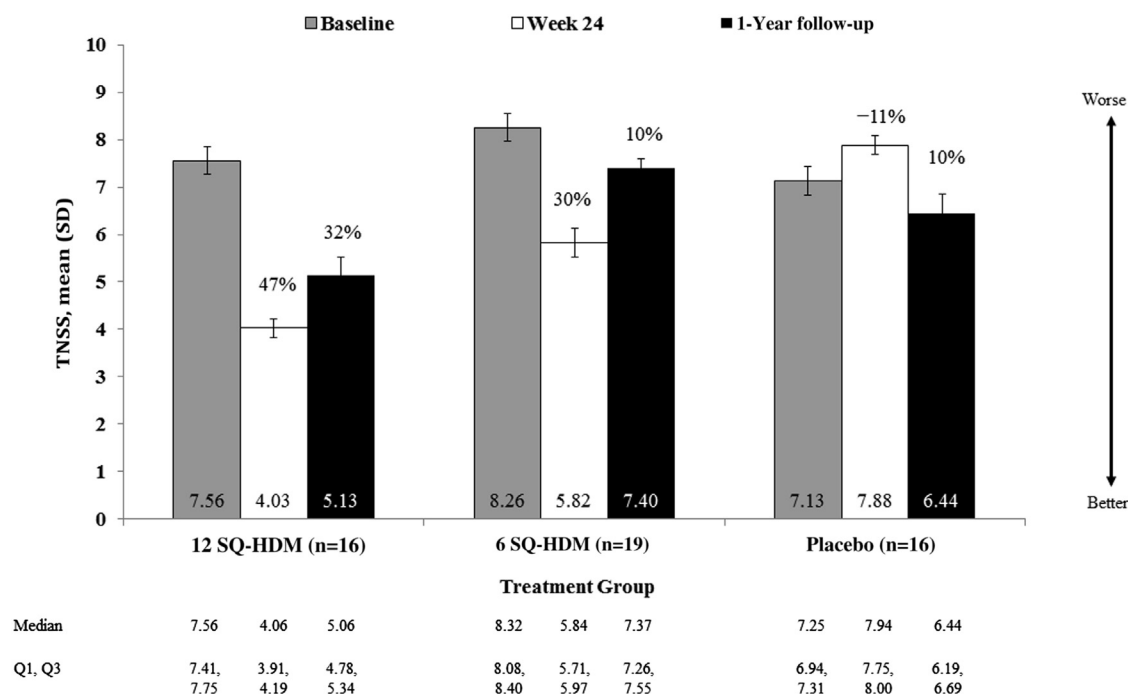


Figure 1. Mean total nasal symptom score (TNSS) at baseline, week 24, and 1-year follow-up (all participants with follow-up). Percentages represent improvements relative to baseline. IQR, interquartile range; HDM, house dust mite.

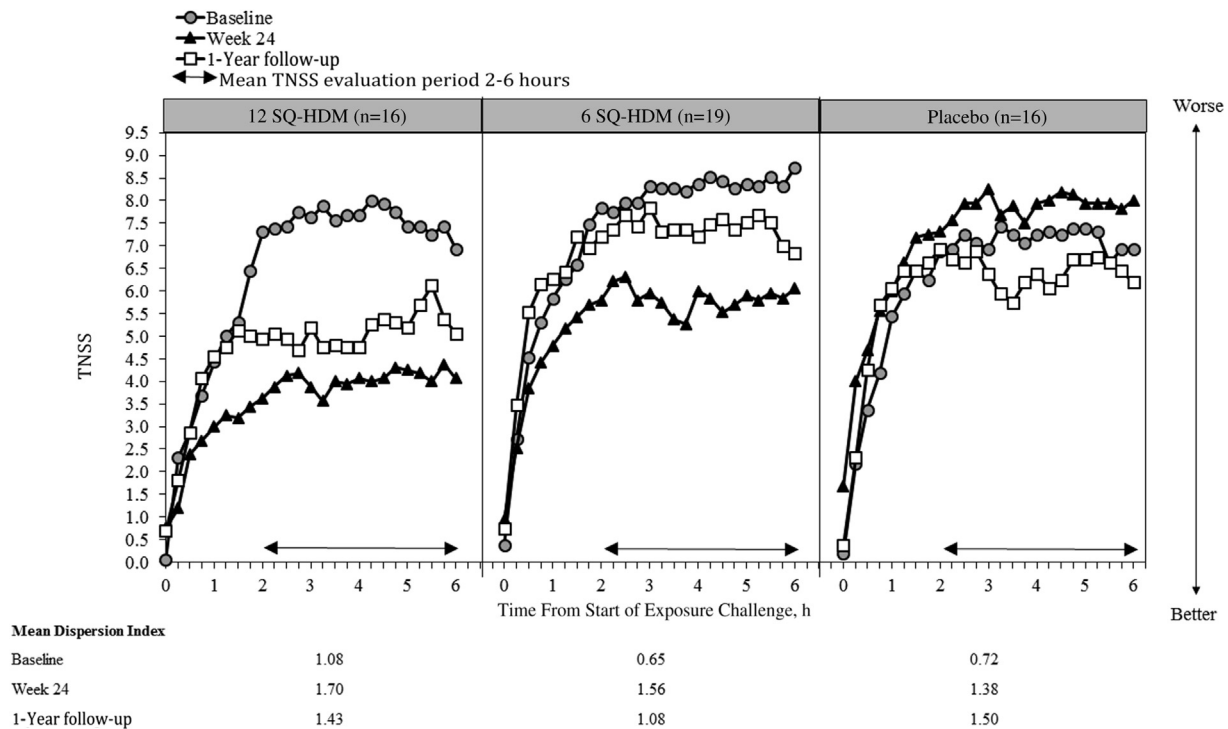


Figure 2. Total nasal symptom score (TNSS) during the baseline and 1-year follow-up exposure challenges (all participants with follow-up). HDM, house dust mite.

patients with asthma who experienced 1 or more treatment-emergent adverse events compared with those without asthma (93% and 83%, respectively); however, none were severe or serious asthma worsenings. The incidence of the most common treatment-related adverse events in those with and without asthma is given in eTable 1. There were no acute asthma exacerbations or asthma

events of severe intensity in the patients with or without asthma. One patient with asthma receiving 12 SQ-HDM experienced an asthma event from days 94 to 142, which was treated with albuterol as needed. The event was assessed as moderate and not related to treatment.

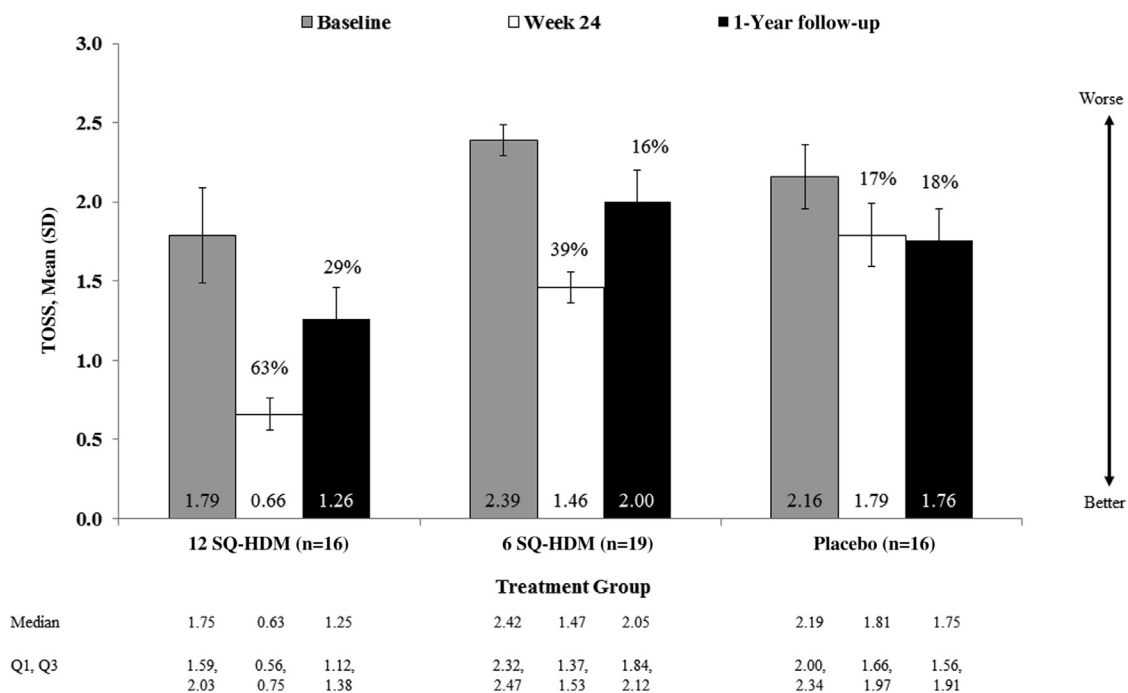


Figure 3. Mean total ocular symptom score (TOSS) at baseline, week 24, and 1-year follow-up (all participants with follow-up). Percentages represent improvements relative to baseline. Q1, Q3, interquartile range; HDM, house dust mite.

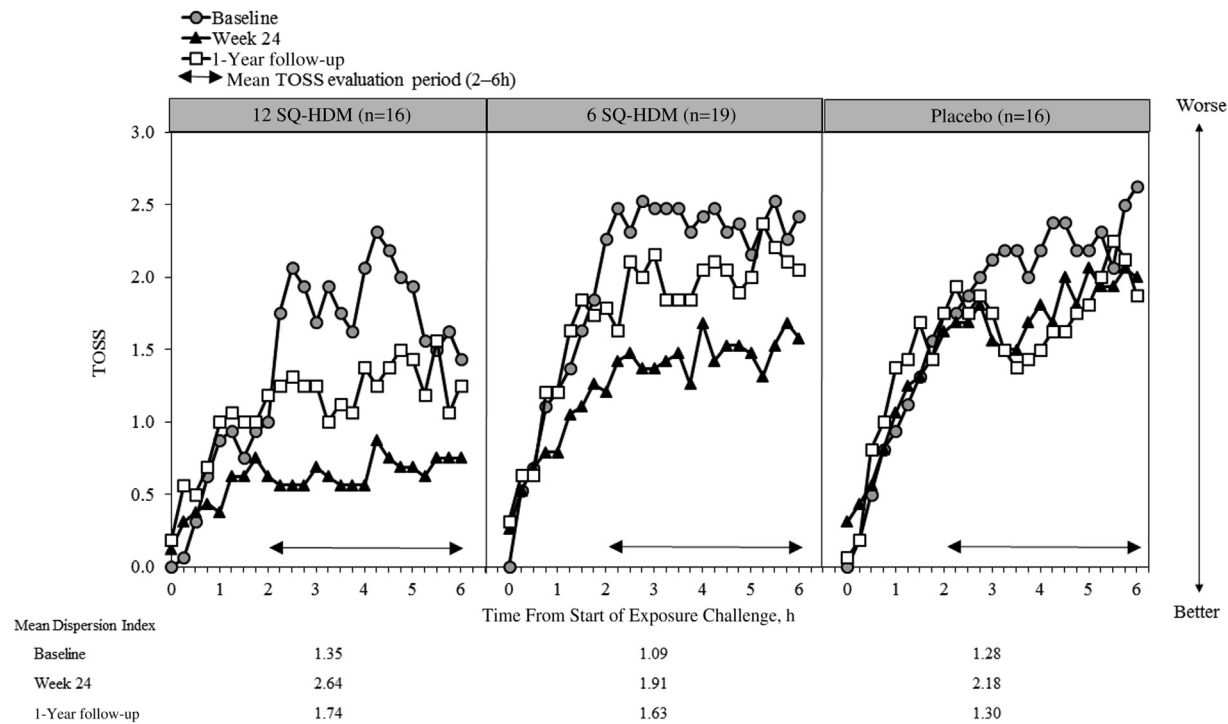


Figure 4. Total ocular symptom score (TOSS) during the baseline, week 24, and 1-year follow-up exposure challenges (all participants with follow-up). HDM, house dust mite.

Eight participants (3 in the 12 SQ-HDM group and 5 in the placebo group) experienced decreases in either FEV₁ or PEF measurements during the exposure chamber sessions and were discontinued from the trial. An insignificant association was found between larger decreases in percentage predicted FEV₁ during the exposure challenge and higher asthma symptom scores. No clinically meaningful differences were found between treatment groups

in the change from baseline in FEV₁, forced vital capacity, and PEF during the 24-week original trial or at follow-up.

Discussion

Approximately 1 year after finishing the 24 week treatment period, participants who had received 12 SQ-HDM still had markedly lower nasal and ocular symptoms compared with baseline and

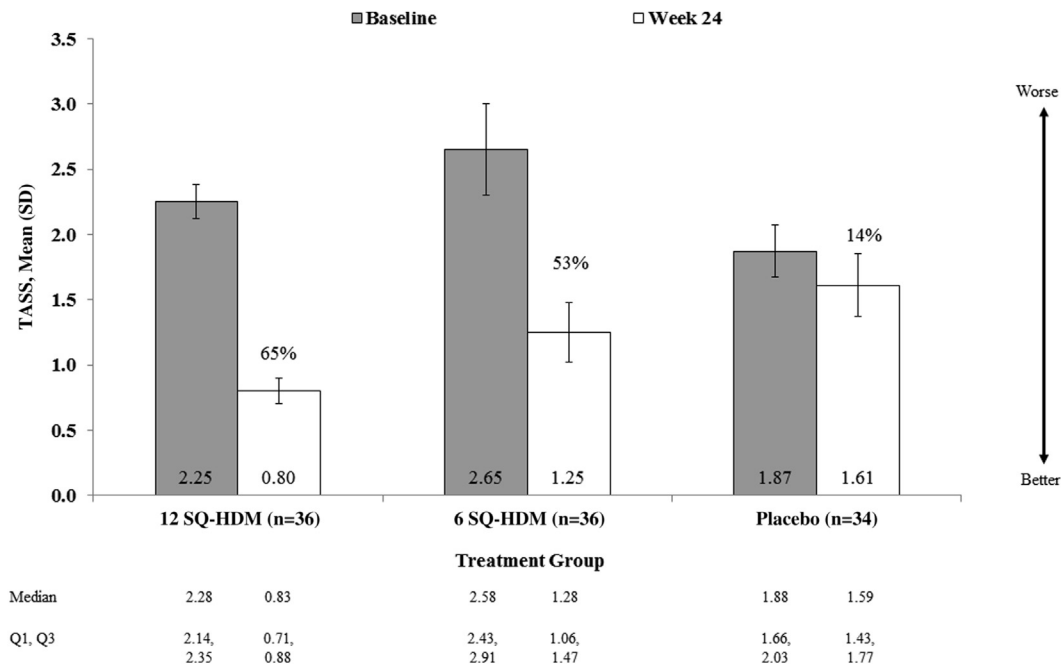


Figure 5. Mean total asthma symptom score (TASS) at baseline and week 24 (trial completers). Percentages represent improvements relative to baseline. HDM, house dust mite; Q1, Q3, interquartile range.

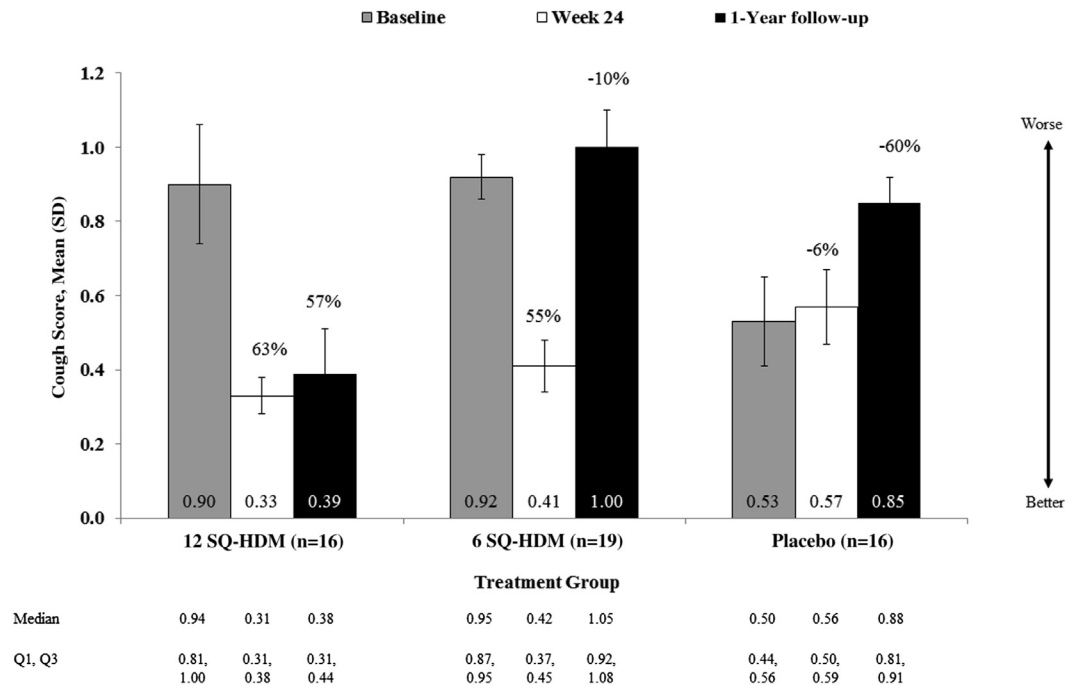


Figure 6. Mean cough score at baseline, week 24, and 1-year follow-up (all participants with follow-up). Percentages represent improvements relative to baseline. IQR, interquartile range; HDM, house dust mite.

placebo when challenged in an EEC. The TASS, which included cough, wheeze, and dyspnea, was improved from baseline after 24 weeks of HDM SLIT tablet treatment. Cough was the only asthma symptom measured at both week 24 and at the 1-year follow-up, and improvement with 12 SQ-HDM treatment compared with baseline was observed at both timepoints. The improvement in rhinoconjunctivitis and asthma symptoms observed at week 24 with 6 SQ-HDM were not as evident as those observed with 12 SQ-HDM and did not appear to be retained at the 1-year follow-up. Together, these data indicate that nasal, ocular, and asthma symptoms are improved with 12 SQ-HDM and that 24 weeks of treatment produces a durable effect of up to 1 year.

The persistent improvement in symptoms approximately 1 year after stopping 12 SQ-HDM treatment was observed after a treatment period of only 24 weeks. Allergen immunotherapy guidelines recommend a treatment duration of at least 3 years.¹⁸ Furthermore, an open-label, pharmacotherapy controlled trial of HDM SLIT drops revealed that beneficial effects persisted for 7 years in individuals receiving 3 years of treatment and 8 years in individuals receiving 4 to 5 years of treatment. Thus, the long-term treatment effect of 12 SQ-HDM may be extended even farther than 1 year if the treatment period were longer than 24 weeks. The demonstrated long-term treatment effect of 12 SQ-HDM could have a clinical and economic effect.

The 1-year follow-up data are limited by the small number of individuals in the analysis. The follow-up challenge visit was not a planned part of the original EEC trial but was rather a part of the Vienna Challenge Chamber's annual diagnosis update of allergic individuals. Although measurement of nasal and ocular symptoms was consistent between the designated trial end points and the 1-year follow-up challenge, only cough was measured at the 1-year follow-up. Therefore, no direct comparison was available among TASS at baseline, week 24, and the 1-year follow-up.

The observed improvement in asthma symptoms with 12 SQ-HDM at week 24 supplements previous data regarding the beneficial effect of the SQ HDM SLIT-tablet on asthma. In a double-

blinded, placebo-controlled trial of 604 individuals with mild to moderate HDM asthma requiring ICS use, 1 year of treatment with the 6 SQ-HDM dose reduced the mean ICS dose needed to maintain asthma control by 42%.¹⁴ The 12 SQ-HDM dose was not studied. In a double-blinded, placebo-controlled trial of 834 patients with HDM asthma that was not well controlled by medium- to high-dose ICSs, up to 18 months of treatment with 12 SQ-HDM significantly decreased time to first asthma exacerbation after the ICS dose was reduced.¹⁵ Collectively, these data support SQ HDM SLIT-tablets as an effective treatment option for HDM asthma, and in 2015 the tablets were approved for this indication in Europe.

These post hoc data from an EEC trial indicate that a sustained benefit of 12 SQ-HDM for rhinoconjunctivitis and cough symptoms was observed approximately 1 year after the end of a 24-week treatment period. Furthermore, asthma symptoms were improved after 24 weeks of treatment with the HDM-SLIT tablet. The data are promising; nevertheless, the sustained benefit should be confirmed in a prospectively designed study with follow-up longer than 1 year after discontinuation.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.10.015>.

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Supplementary Data

eTable 1

Treatment-Related AEs Reported by 5% or More of the Study Participants With or Without Asthma in Either Treatment Group

AE	With Asthma			Without Asthma		
	12 SQ-HDM (n = 10), %	6 SQ-HDM (n = 11), %	Placebo (n = 9), %	12 SQ-HDM (n = 32), %	6 SQ-HDM (n = 30), %	Placebo (n = 32), %
Any treatment-related AE	100	64	0	69	60	6
Throat irritation	60	27	0	50	37	0
Mouth edema	10	46	0	28	17	0
Lip swelling	20	0	0	16	7	3
Oral pruritus	20	18	0	13	13	0
Dyspepsia	10	0	0	9	3	0
Dyspnea	10	0	0	0	0	0
Ear pruritus	10	0	0	6	0	0
Oropharyngeal pain	0	9	0	0	0	0
Oropharyngeal swelling	0	0	0	6	0	0
Swollen tongue	0	0	0	6	0	0
Pharyngeal edema	10	9	0	3	0	0
Oral discomfort	0	9	0	0	0	0
Tongue pruritus	0	9	0	0	0	0
Lip blister	10	0	0	0	0	0
Glossitis	10	0	0	0	0	0
Eye pruritus	0	9	0	0	0	0

Abbreviations: AE, adverse event; HDM, house dust mite.