

SQ house dust mite sublingual immunotherapy tablet subgroup efficacy and local application site reaction duration



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ABSTRACT

Background: Allergic rhinitis with or without conjunctivitis (AR/C) is common, necessitating evaluation of SQ house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet efficacy in various subgroups.

Objective: To evaluate 12 SQ-HDM efficacy and safety across subgroups, and the onset, duration, and recurrence of local application site reactions.

Methods: Subgroup (age, sex, race, asthma status, and allergen sensitization) efficacy was assessed using pooled data from 2 previously described trials of daily 12 SQ-HDM vs placebo for AR/C (n = 2,138). Efficacy was measured by average total combined rhinitis score (TCRS; rhinitis daily symptom plus medication score) during the last 8 weeks of treatment. Safety in subgroups and local application site reaction onset, duration, and recurrence were evaluated using pooled data from 5 previously described trials of SQ HDM SLIT-tablet (n = 2,923).

Results: Significant (based on 95% confidence intervals [CIs]) reduction in TCRS was seen with 12 SQ-HDM relative to placebo across all subgroups, with TCRS improvements ranging from 15% to 25%. The AE profile was generally similar within subgroups. Approximately 95% of local application site reactions were mild to moderate in severity. Median duration on day 1 of treatment for the most common local application site reactions (throat irritation, oral pruritus, ear pruritus, and lip swelling) ranged from 30 to 60 minutes; median first day of onset ranged from days 1 to 4 of treatment; median days that reactions recurred ranged from 3 to 12 days.

Conclusion: Treatment with 12 SQ-HDM consistently improved symptoms and was well tolerated in relevant subgroups of subjects with HDM AR/C. Local application site reactions to 12 SQ-HDM were typically mild to moderate and transient.

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Introduction

Several clinical trials have demonstrated the beneficial effects of SQ house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet on allergic rhinitis with or without conjunctivitis (AR/C) and on allergic asthma.^{1–5} Global Initiative for Asthma guidelines now recommend add-on HDM SLIT for patients with HDM asthma (currently no indication in the United States or Canada) and allergic rhinitis who have asthma exacerbations despite inhaled corticosteroid (ICS) treatment (as long as forced expiratory volume in 1 second [FEV₁] is >70% predicted).⁶ However, physicians and health care providers may have some practical questions concerning the SQ HDM SLIT-tablet when considering immunotherapy options for patients. Allergic rhinitis with or without conjunctivitis is a common disease, affecting people throughout the world regardless of age, sex, or race. It is also frequently found to be concomitant with asthma. Sublingual immunotherapy tablets for grass have been shown to be effective for AR/C in subgroups, including multisensitized patients and patients with asthma.^{7,8} However, data regarding the efficacy of SQ HDM SLIT-tablet in age, sex, race, asthmatic status, and sensitization status subgroups are lacking.

Sublingual immunotherapy in general, including SQ HDM SLIT-tablets, is known to be associated with mild to moderate local application site reactions (LASR), such as oral pruritus and throat irritation.^{9,10} In SLIT-tablet clinical trials, 4% to 7% of subjects discontinued because of treatment-related adverse events (AEs).⁹ Treatment-related AEs are the most common clinical reason why patients discontinue within the first few months of SLIT treatment in clinical practice.¹¹ Information regarding the duration and recurrence of LASR may reduce patient concerns and improve acceptability and adherence to SLIT treatment. Therefore, the duration and nature of LASR associated with SQ HDM SLIT-tablet are key questions for prescribers and patients.

The objective of these analyses was to evaluate the efficacy and safety of SQ HDM SLIT-tablet across subgroups of interest in subjects with HDM AR/C, and the duration and recurrence of LASR. Subgroup efficacy was assessed by using pooled data from 2 similarly designed trials that evaluated the efficacy of 12 SQ-HDM for AR/C. Local application site reactions' duration and recurrence were evaluated using pooled data from trials that evaluated the safety of SQ HDM SLIT-tablets.

Methods

Trial Descriptions

In all, data from 5 trials of SQ HDM SLIT-tablet (ALK-Abelló A/S, Hørsholm, Denmark) were included in this analysis, although the 12 SQ-HDM dose was only evaluated in 4 of the trials. Efficacy data for the current analysis were obtained from 2 randomized, double-blinded, multicenter trials conducted in subjects with HDM AR/C (P001 and MT-06). P001 was a trial of up to 52 weeks (NCT01700192) conducted in North American subjects aged 12 years or older,³ and MT-06 was a 52-week trial (NCT01454544) conducted in European subjects aged 18 to 65 years.¹ Detailed inclusion and exclusion criteria have been previously described.^{1,3}

Safety data were pooled from P001 and MT-06, as well as 3 other randomized, double-blinded trials that evaluated SQ HDM SLIT-tablet safety (MT-02, MT-04, and P003). MT-02 was a 52-week trial (NCT00389363) conducted in European subjects aged 14 years or older with HDM asthma requiring ICS use, and with HDM AR/C.² MT-02 evaluated doses of 1, 3, or 6 SQ-HDM or placebo. Because 12 SQ-HDM was not evaluated in MT-02, only the placebo arm was included in the pool of the current analysis. MT-04 was a trial of up to 18 months (clinicaltrialsregister.eu, 2010-018621-19) conducted in European subjects aged 18 years or older with a primary diagnosis of HDM asthma that was not well controlled by ICS, and

with HDM AR/C.⁵ P003 was a 24-week environmental chamber trial (NCT01644617) conducted in European subjects aged 18 years or older with a primary diagnosis of HDM AR/C with or without asthma.⁴ Detailed inclusion and exclusion criteria have been previously described.^{2,4,5}

Subjects in the trials received daily SQ HDM SLIT-tablet or placebo. "SQ" represents a method for standardization on biological potency, major allergen content, and complexity of the allergen extract. The 6 SQ-HDM dose was also evaluated in MT-02, MT-06, MT-04, and P003, but was not included in this analysis because the approved dose in Europe and North America is 12 SQ-HDM.¹² The 12 SQ-HDM dose contains a total of 30 µg major allergen, comprising approximately 15 µg group 1 allergens (Der f 1 and Der p 1 combined) and approximately 15 µg group 2 allergens (Der f 2 and Der p 2 combined).¹³ Open-label symptom-relieving medications were provided in all trials but were not allowed as pre-medication to reduce AEs so that the safety and tolerability profile could be accurately captured.

Institutional review boards or ethics committees approved the protocols, and written informed consent was obtained from the subject or subject's legal representative.

Assessments

In the randomized, double-blinded, multicenter trials of subjects with AR/C (trials P001 and MT-06), the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment was the primary end point. Total combined rhinitis score is the sum of the rhinitis daily symptom score (DSS) and rhinitis daily medication score (DMS), and was scored as previously described.^{1,3}

Data on AEs were collected in all 5 trials by general questioning at study visits regarding whether the patient had experienced AEs since the last visit. In addition, in P001, data on the presence of local AEs identified by the World Allergy Organization¹⁴ were collected daily for the first approximately 28 days of treatment, using closed-ended questions in a patient questionnaire.¹⁵ The AE data from the 12 SQ-HDM dose in the 4 trials that evaluated the 12 SQ-HDM dose were pooled; placebo data were pooled from all 5 trials. Data on duration in minutes on the first day of treatment for LASR, as well as day of onset and the number of days each local application site reaction recurred, were analyzed.

Statistical Analysis

In P001, prespecified between-treatment comparisons for TCRS were performed using the Wilcoxon rank sum test, and the Hodges-Lehmann estimate of treatment difference was calculated. Differences in percentages were calculated based on medians. In MT-06, prespecified between-treatment comparisons for TCRS were performed using an analysis of covariance with the square root transformed average TCRS as response, the square root transformed AR symptom score at baseline as a covariate, treatment as a fixed factor, and country as a random factor and adjusted for different error variation for each treatment group. Differences in percentages were calculated based on back-transformed adjusted means.

The TCRS data for the 12 SQ-HDM and placebo doses from P001 and MT-06 were pooled post hoc for subgroup analysis and analyzed by means of an analysis of covariance with square root transformed values as response. Trial, treatment, subgroup, treatment-by-subgroup interaction, and baseline asthma status (except in the asthma subgroup analysis) were included as fixed factors; the square root transformed AR symptom score at baseline was included as a covariate, and a different residual error variance was specified by treatment group. Adjusted means were back-transformed by taking the square. Subgroups examined were categorized by age, sex, race, baseline asthma status, and allergen sensitization. The percentage

improvement in TCRS relative to placebo was calculated using the equation: (placebo – 12 SQ-HDM)/placebo $\times$ 100.

Results

Efficacy and Safety in Subgroups

In all, 2,138 subjects were included in the efficacy analysis, and 2,923 were included in the safety analysis. Demographics and disease characteristics of the randomized pooled populations are shown in Table 1.

In the 2 randomized, double-blind, multicenter trials for AR/C (P001 and MT-06), treatment with 12 SQ-HDM significantly improved TCRS 17% and 18%, respectively, vs placebo (Fig 1; both $P \leq .001$). Across the subgroups, TCRS with 12 SQ-HDM were consistently significantly reduced compared with those with placebo (Fig 2). The lowest observed TCRS improvement was 15% in subjects

without asthma, and the greatest improvement was 25% in subjects aged 12 to 17 years (Fig 2).

The AE profile from pooled data of all 5 trials was generally similar among subgroups (Table 2). The incidence of treatment-related AEs in the 12 SQ-HDM appeared numerically higher in subjects aged 12 to 17 years vs 18 to 49 years (92% vs 68%, respectively). This is likely attributable to the fact that the 12- to 17-year subgroup comprised only subjects in the P001 trial, in which prespecified local AEs were actively solicited daily for approximately the first 28 days of treatment via a questionnaire. This hypothesis is supported by the higher incidence of treatment-related AEs in the subjects aged 12 to 17 years vs 18 to 49 years treated with placebo (43% vs 26%, respectively; Table 2). Within the P001 trial alone, the incidence of treatment-related AEs with 12 SQ-HDM was 93% in subjects aged 12 to 17 years, 84% in subjects aged 18 to 49 years, and 77% in subjects aged 50 years or older.

Onset, Duration, and Recurrence of AEs

In the total pooled safety population, the incidence of treatment-emergent AEs was 83% with 12 SQ-HDM and 64% with placebo, and the incidence of treatment-related AEs was 69% with 12 SQ-HDM and 28% with placebo (Table 2). The percentage of subjects who discontinued because of treatment-related AEs was 7% with 12 SQ-HDM and 1% with placebo (Table 2). Approximately 95% of the LASR were assessed as mild to moderate in severity.

The most common treatment-related AEs (incidence of >10%) with 12 SQ-HDM were throat irritation, oral pruritus, ear pruritus, and lip swelling. Overall, in the 12 SQ-HDM treatment group, the onset of prespecified LASR ranged from a median of 1 (first day of treatment) to 4 days after treatment initiation (Table 3). The median duration of these common treatment-related LASR on the first day of treatment ranged from 30 to 60 minutes with 12 SQ-HDM treatment (Table 3). The median number of days that treatment-related LASR recurred ranged from 3 to 12 days with 12 SQ-HDM treatment (Table 3).

Overall Safety

No reports were made of anaphylactic shock or death. The occurrence of serious AEs was low and occurred at a similar frequency

Table 1
Demographics and Disease Characteristics of Randomized Subjects in the Pooled Population from Trials P001, MT-02, MT-06, MT-04, and P003

	12 SQ-HDM (n = 1,383)	Placebo (n = 1,540)
Female, n (%)	754 (55)	812 (53)
Mean age $\pm$ SD (range), y	33.8 $\pm$ 12.7 (12–77)	33.6 $\pm$ 12.7 (12–85)
White, n (%)	1,195 (86)	1,347 (88)
Subjects with asthma, n (%)	686 (50)	825 (54)
IgE sensitization type, n (%)		
HDM only	394 (29)	415 (27)
HDM and other allergens	987 (71)	1,117 (73)
Not sensitized to HDM ^a	2 (0.1)	8 (0.5)
Mean <i>D. farinae</i> SPT wheal size $\pm$ SD, mm	10.8 $\pm$ 4.3	10.1 $\pm$ 4.5
Mean <i>D. pteronyssinus</i> SPT wheal size $\pm$ SD, mm	10.9 $\pm$ 4.4	10.4 $\pm$ 4.4
Mean <i>D. farinae</i> serum-specific IgE $\pm$ SD, kU _A /L	24.4 $\pm$ 44.4	24.3 $\pm$ 34.8
Mean <i>D. pteronyssinus</i> serum-specific IgE $\pm$ SD, kU _A /L	24.7 $\pm$ 46.2	25.3 $\pm$ 41.2

Abbreviations: HDM, house dust mite; IgE, immunoglobulin E; SD, standard deviation; SPT, skin prick test.

^aProtocol violators.

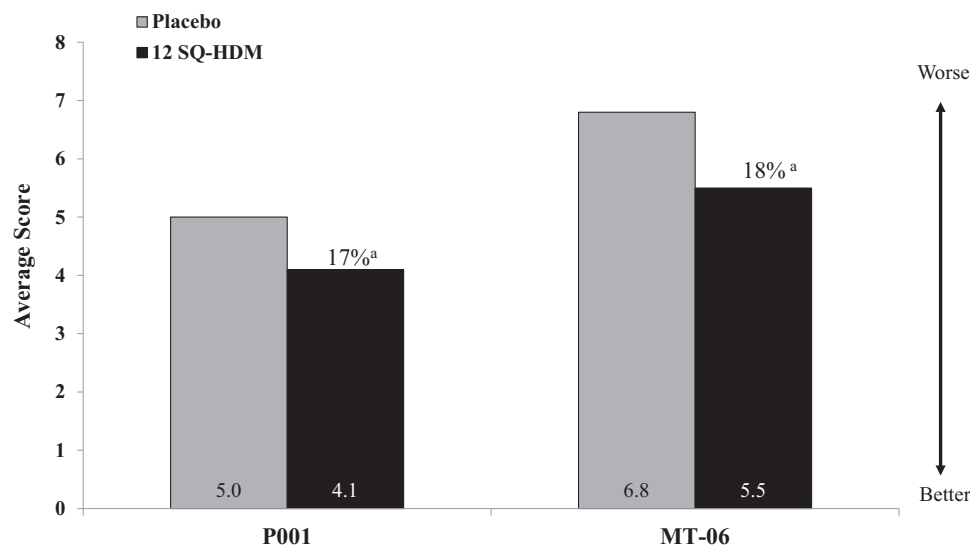


Figure 1. Average TCRS for total populations during approximately the last 8 weeks of treatment in P001 and MT-06. Plots indicate average score medians for P001 and least square means for MT-06. Percentages indicate the improvement in scores relative to placebo. ^a $P \leq .001$ vs placebo. HDM, house dust mite; TCRS, total combined rhinitis score.

Table 2

Summary of Adverse Events in Subgroups Using Pooled Data From Trials P001, MT-02, MT-06, MT-04, and P003

Subpopulation	Any TEAE, %	Any TRAE, %	Serious TRAE, %	Discontinued because of TRAE, %
Total population				
12 SQ-HDM (n = 1,383)	83	69	0.2 ^a	7
Placebo (n = 1,540)	64	28	0.1	0.8
Aged 12 to 17				
12 SQ-HDM (n = 95)	94	92	0	10
Placebo (n = 106)	78	43	0	0
Aged 18 to 49				
12 SQ-HDM (n = 1,105)	82	68	0.2	7
Placebo (n = 1,247)	62	26	0.2	0.8
Aged 50 to 64				
12 SQ-HDM (n = 169)	79	61	0.6	4
Placebo (n = 164)	68	31	0	0.6
Aged ≥65 years				
12 SQ-HDM (n = 14)	93	57	0	0
Placebo (n = 23)	78	39	0	4
Male				
12 SQ-HDM (n = 629)	80	64	0.2	5
Placebo (n = 728)	60	23	0.1	0.8
Female				
12 SQ-HDM (n = 754)	86	73	0.3	8
Placebo (n = 812)	67	32	0.1	0.7
White				
12 SQ-HDM (n = 1,195)	82	68	0.2	7
Placebo (n = 1,347)	63	25	0.1	0.8
Nonwhite				
12 SQ-HDM (n = 185)	86	76	0.5	6
Placebo (n = 189)	71	45	0	0.5
With asthma				
12 SQ-HDM (n = 686)	82	62	0.1	8
Placebo (n = 825)	64	23	0.2	1
Without asthma				
12 SQ-HDM (n = 697)	84	75	0.3	6
Placebo (n = 715)	64	32	0	0.6
Monosensitized				
12 SQ-HDM (n = 394)	78	64	0	5
Placebo (n = 415)	56	23	0	0.7
Polysensitized				
12 SQ-HDM (n = 987)	85	71	0.3	7
Placebo (n = 1,117)	66	29	0.2	0.8

Abbreviations: HDM, house dust mite; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

^aTwo subjects had accidental overdose, considered serious per the study protocol, but did not meet International Conference on Harmonization criteria for seriousness.

between the 12 SQ-HDM and placebo groups (Table 2). One nonserious, treatment-related systemic allergic reaction of moderate intensity in the 12 SQ-HDM group occurred on day 1 under medical supervision that was managed with conventional treatment (including epinephrine). No reports were made of serious local allergic swelling, and no events resulted in airway compromise. The general safety profile in AR/C and asthma subjects was similar.

Discussion

In a pooled analysis of data from 2 similarly designed trials, 12 SQ-HDM significantly improved symptoms in relevant subgroups of subjects with HDM AR/C defined by age, sex, race, asthma status, and sensitization to non-HDM aeroallergens. Safety analysis of pooled data indicated that 12 SQ-HDM was well tolerated, and the AE profile was similar among the subgroups. Furthermore, pooled analyses also indicated that the most common LASR were transient, generally lasting less than 60 minutes and recurring for less than 2 weeks.

The demonstrated efficacy of 12 SQ-HDM for AR/C among various relevant subgroups has clinical management implications. Unlike many diseases, AR/C affects males and females of all ages and races. The current analysis indicates that 12 SQ-HDM is a viable AR/C treatment option regardless of sex, age, or race.

Table 3Median Day of Onset, Duration (Minutes on Day 1 of Treatment), and Recurrence^a of the Most Common Local Application Site Reactions Using Pooled Data From Trials P001, MT-02, MT-06, MT-04, and P003

Adverse event	12 SQ-HDM (n = 1,383)	Placebo (n = 1,540)
Throat irritation		
Onset		
Median day (range)	1 (1–348)	2 (1–267)
No. of subjects with data	603	192
Duration		
Median minutes (range)	42 (1–870)	45 (1–810)
No. of subjects with data	460	94
Recurrence		
Median days (range)	12 (1–377)	3 (1–384)
No. of subjects with data	596	189
Oral pruritus		
Onset		
Median day (range)	1 (1–304)	2 (1–225)
No. of subjects with data	594	131
Duration		
Median minutes (range)	30 (1–826)	60 (1–1,149)
No. of subjects with data	414	62
Recurrence		
Median days (range)	12 (1–532)	3 (1–464)
No. of subjects with data	588	128
Ear pruritus		
Onset		
Median day (range)	1 (1–367)	4 (1–190)
No. of subjects with data	413	95
Duration		
Median minutes (range)	30 (1–624)	60 (5–600)
No. of subjects with data	289	30
Recurrence		
Median days (range)	10 (1–376)	3 (1–313)
No. of subjects with data	411	93
Lip swelling		
Onset		
Median day (range)	4 (1–273)	4 (1–164)
No. of subjects with data	188	23
Duration		
Median minutes (range)	60 (10–864)	15 (15–15)
No. of subjects with data	49	4
Recurrence		
Median days (range)	3 (1–379)	3 (1–144)
No. of subjects with data	184	23

Abbreviation: HDM, house dust mite.

^aDoes not imply a continuous duration, but rather a recurrence on subsequent days.

Furthermore, 12 SQ-HDM improved symptoms in subjects with asthma, a common comorbid condition of AR/C, and in patients who were multisensitized to allergens other than HDM. In years past, monosensitized patients were hypothesized to be more likely than polysensitized patients to experience benefits of allergy immunotherapy.¹⁶ However, most (75% or more) patients with AR/C are multisensitized,¹⁷ and a SLIT product that was not efficacious in this subgroup would limit its use. The results of the current analysis for the SQ HDM SLIT-tablet are consistent with a post-hoc pooled analysis of trials for timothy grass SLIT-tablet and a post-hoc analysis of a single trial of 5-grass SLIT-tablet, which also found that treatment was similarly efficacious between multisensitized and monosensitized subjects.^{7,8} Also in a pooled analysis of 2 trials for ragweed SLIT-tablet, a numeric trend was seen toward greater efficacy in multisensitized vs monosensitized subjects (total combined score [sum of daily symptom score and daily medication score] improvement 27% vs 19%, respectively, for the approved dose).¹⁸

The AE profile was similar among the subgroups, including the subgroup of patients with asthma. The safety of SLIT-tablets in patients with asthma has been an area of interest because the presence of asthma has been identified as a risk factor for serious systemic reactions with subcutaneous immunotherapy.^{19,20} Results from the current analysis and pooled analyses of timothy grass and ragweed

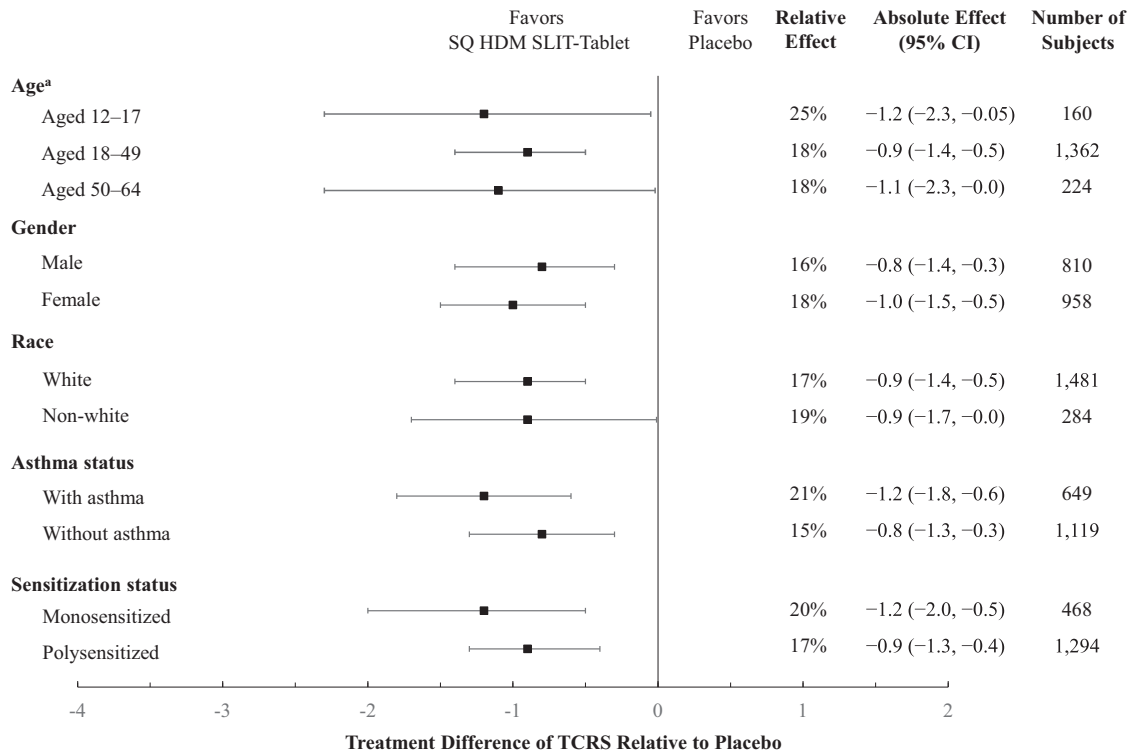


Figure 2. Treatment difference in average TCRS during approximately the last 8 weeks of treatment in various subgroups, using pooled data from trials P001 and MT-06. HDM, house dust mite; TCRS, total combined rhinitis score. ^aSubgroup of subjects aged ≥ 65 years was not analyzed because there were too few subjects in this group.

SLIT-tablet trials have not found evidence of altered safety profiles in patients with asthma vs patients without asthma, with the caveat that all of the SLIT-tablet trials included in the pooled analyses (except MT-04) only enrolled subjects with controlled (FEV_1 percent predicted $\geq 70\%$) mild to moderate asthma.^{21,22} One age subgroup (12–17 y) did appear to have a higher incidence of treatment-emergent and treatment-related AEs compared with the other subgroups. However, the higher incidence is likely because the 12- to 17-year subgroup comprised only subjects from the P001 trial. In the P001 trial, the occurrence of prespecified LASR was actively solicited using a daily questionnaire. Frequencies of AEs have been shown to increase when reporting of specific AEs is intentionally solicited, which may be attributable to a suggestive effect, creating a feeling of a symptom.^{23–25} Examination of the 12 SQ-HDM AE profile between data collected in P001 and trials in which subjects were not questioned regarding the presence or absence of specific AEs did not reveal any qualitative differences.²⁶

Patients who are unprepared for the LASR associated with SLIT treatment may experience an unpleasant feeling, become alarmed, and prematurely discontinue treatment. Across SLIT-tablet trials, 4% to 7% of patients discontinued treatment because of AEs.⁹ Thus, it is critical to educate patients regarding the potential occurrence of LASR and provide information on how long these reactions may last. The current analysis indicates that the most common LASRs associated with 12 SQ-HDM generally occur during the first few days of treatment, last less than an hour, and recur for less than 2 weeks. These data should reassure patients that LASR to SQ HDM SLIT-tablet are typically mild to moderate and often are transient.

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