Pooled efficacy and safety data for house dust mite sublingual immunotherapy tablets in adolescents

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Abstract
Background: House dust mite (HDM) respiratory allergy is a common and burdensome disease in children and adolescents. There are few HDM allergy immunotherapy trials in children with perennial allergic rhinitis. This post hoc analysis used pooled data to evaluate efficacy and safety of the SQ HDM sublingual immunotherapy (SLIT) tablet in adolescents (12-17 years).

Methods: In two double-blind, placebo-controlled trials conducted in North America and Japan, respectively, subjects aged 12+ years with HDM allergic rhinitis were randomized to up to 1 year of treatment. The primary end-point in both trials was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment in the active group compared with placebo. Data from subjects aged 12-17 years were pooled (N=395).

Results: In the pooled adolescent subpopulation, average TCRS improved 22% with 12 SQ HDM vs placebo (absolute treatment difference of 1.04; \( P < 0.01 \)). Rhinitis daily symptom score (DSS), conjunctivitis DSS and rhinitis daily medication score (DMS) were also significantly improved vs placebo in the pooled adolescent subpopulation (all \( P < 0.05 \)). There were no new safety signals for adolescents. The frequency of adverse events was similar in adolescents and adults with the majority being mild application site-related events.

Conclusions: Treatment with 12 SQ HDM appears to be effective and well tolerated in adolescents with HDM allergic rhinitis.

KEYWORDS
adolescent, allergic rhinitis, allergy immunotherapy, house dust mite, SLIT-tablet, sublingual immunotherapy

INTRODUCTION

Allergic rhinitis is estimated to affect 17%-29% of the population across Europe and is found in all ethnic groups and ages. A survey of children and adolescents found that allergies generally had significant negative effects on physical and mental health compared to children/adolescents without allergies with 40% of parents, indicating that allergies affected their child’s school performance and 21% reported their child’s work or other activities were limited by allergies. Allergy to house dust mite (HDM) is prevalent in children and adolescents and has notable clinical implications. Allergy immunotherapy is the only treatment for allergies that can alter the underlying pathologic disease mechanisms. Yet, HDM allergy immunotherapy for allergic respiratory diseases (ie, allergic rhinitis and allergic asthma) is poorly documented in adolescents, and in particular, there is a lack of large, multicenter trials with well-characterized, standardized HDM...
allergen extracts. Recently, new trials with sublingual tablet formulations examining dosing, treatment onset, effect size, and quality of life in both patients with allergic rhinitis and allergic asthma have been conducted.

The SQ HDM SLIT-tablet (ALK, Denmark) is a once-daily fast-dissolving formulation (oral lyophilisate) containing standardized HDM allergen extract. SQ HDM SLIT-tablets have demonstrated clinical benefit in adults with HDM allergic rhinitis (with or without conjunctivitis) and HDM allergic asthma. One safety trial conducted in adolescents found that SQ HDM SLIT-tablets were well tolerated. Among trials that evaluated the efficacy and safety of SQ HDM SLIT-tablet for the treatment of moderate-severe HDM allergic rhinitis, 2 trials included adolescent subpopulations (aged 12-17 years). The objective of this post hoc analysis was to use pooled data from these 2 previously published trials to evaluate the efficacy and safety of SQ HDM SLIT-tablets in the adolescent subpopulation.

2 METHODS

2.1 Trial designs

Two randomized, parallel-group, double-blind, placebo-controlled, multisite, phase 3 trials were conducted investigating the efficacy and safety of the SQ HDM SLIT-tablet in HDM allergic subjects. One trial was conducted in North America (trial A; clinicaltrials.gov identifier NCT01700192) and 1 trial was conducted in Japan (trial B; JapicCTI number 121848). Both trials have been previously described. The trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2 Subject selection criteria

Subjects in both trials were adolescents and adults (12-85 years of age in trial A and 12-64 years of age in trial B) with a history of moderate-severe HDM allergic rhinitis and with a history of prior pharmacologic treatment for HDM allergic rhinitis in the previous year before the screening visit.

In trial A, subjects were required to be sensitized to HDM with a positive skin test ≥5 mm compared with saline control and serum specific IgE of ≥0.7 kU/L to either Dermatophagoides (D.) farinae or D. pteronyssinus. Furthermore, subjects were required to demonstrate an allergic rhinitis symptom score above a set threshold (rhinitis daily symptom score [DSS] of at least 6, or a score of at least 5 with one symptom being severe on 5 of 7 consecutive days) before randomization when subjects were expected to have natural exposure to HDM and when allergy-relieving medications were withdrawn. Subjects were randomized between November and March, except for 109 subjects who were randomized based on a positive HDM chamber challenge test. Subjects with FEV<sub>1</sub> < 80% of predicted value or with asthma that required more than a daily medium dose of inhaled corticosteroid were not eligible.

In trial B, subjects were required to be sensitized to HDM based on a positive nasal provocation test and a serum specific IgE of ≥3.5 kU/L to either D. farinae or D. pteronyssinus. Furthermore, subjects were required to have moderate to severe HDM allergic rhinitis symptoms as defined by a rhinitis DSS of at least 7 over at least 7 of the 14 days of the run-in period without any symptomatic treatment. Subjects were randomized between September and November.

2.3 Treatment

The SQ HDM SLIT-tablet is a rapidly dissolving freeze-dried tablet containing a 1:1 mixture of allergen extracts from D. pteronyssinus and D. farinae. The source material consists of bodies and faeces to produce a tablet with the broadest possible spectrum of major and minor allergens from these HDM species. The highly standardized production process for SQ HDM SLIT-tablet ensures a 1:1:1:1 ratio of the Der p 1, Der f 1, Der p 2 and Der f 2 major allergens. The 12 SQ HDM dose contains approximately 15 mcg HDM group 1 allergens (Der f 1 and Der p 1 combined) and 15 mcg HDM group 2 allergens (Der f 2 and Der p 2 combined).

The first tablet was administered at the trial site followed by a 30-minute observation period; subsequent self-administrations were at-home. In trial A, subjects were randomized 1:1 to once-daily treatment with 12 SQ HDM or placebo and treatment was continued for up to 1 year. In trial B, subjects were randomized 1:1:1 to once-daily treatment with 6 SQ HDM, 12 SQ HDM or placebo for 1 year. An updosing regimen was applied in trial B, where all subjects randomized to SQ HDM SLIT-tablets received 2 SQ HDM for the first week after randomization, 6 SQ HDM for the second week (and for the 6 SQ HDM group throughout the trial) and 12 SQ HDM for the third week and throughout the trial (12 SQ HDM group). Treatment duration was approximately 9 months in trial A and 12 months in trial B.

Open-label symptom-relieving medications were provided by the trial sponsors and allowed in trial A when a minimum symptom threshold was met or persistent eye symptoms were present, and in trial B when subjects felt that symptoms were intolerable. Per US FDA regulatory requirement epinephrine auto-injectors were provided to subjects in trial A.

2.4 Assessments

The primary end-point in both trials was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. TCRS was the sum of the rhinitis DSS and rhinitis daily medication score (DMS) with a range of 0-24 points. The rhinitis DSS was the sum of four nasal symptoms (runny nose, blocked nose, sneezing and itchy nose), each rated on a scale from 0 (no symptoms) to 3 (severe symptoms) with a range of 0-12 points. The rhinitis DMS consisted of symptomatic medication scores with a range of 0-12. Secondary end-points were rhinitis DSS, conjunctivitis DSS (sum of gritty feeling/red/itchy eyes and watery eyes) rated on a scale of 0-3, rhinitis DMS and conjunctivitis DMS (range of 0-8). Details of symptom and medication scoring have been previously described. Rhinitis exacerbation days were defined as days with an allergic rhinitis symptom score of 6, or 5 with one individual symptom scored 3 (ie, implying a symptom that was hard to tolerate and caused interference with activities of daily living and/or...
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sleeping). Mild days were defined as days with no individual symptom scored higher than 1 (ie, the symptom was clearly present but caused minimal awareness and was easily tolerated) and no antihistamine use.

Blood samples for the immunologic assessments were collected at baseline and selected visits. Measurements of HDM-specific IgE was performed at ALK, Hørsholm, Denmark, for trial A and at Bio Medical Laboratories (BML) Inc., Kawagoe-shi, Japan, for trial B, by the same procedure.

Participants were monitored for unsolicited adverse events (AEs) and serious adverse events (SAEs) for the duration of the trials. Local adverse events in trial A were solicited by the use of a side effect report card during the first 28 days of treatment, in which subjects reported the presence or absence of local AEs typical of SLIT as identified by the World Allergy Organization. AEs in trial B were assessed by general questioning during site visits.

2.5 | Statistical analysis

The primary efficacy analysis was conducted on the full analysis set (FAS), defined in trial A as all subjects who received at least 1 dose of investigational treatment, and defined in trial B as subjects who entered at least 80% of information regarding symptom score and medication use during the last 8 weeks of treatment. The safety analysis was conducted on all subjects as treated. The TCRS was collected the same way in the 2 trials and was amenable to post hoc data pooling for the 12 SQ HDM dose in the adolescent subgroups (subjects aged 12-17 years). In trial A, the primary efficacy end-point was Hodges-Lehmann estimate with 95% confidence intervals (ie, based on the median TCRS) while in trial B the primary efficacy end-point was based on mean values with a linear mixed-effects model. Pooled adolescent subpopulation data were calculated based on adjusted means using the linear mixed-effects model. Per cent relative treatment difference vs placebo was calculated as (placebo−12 SQ HDM)/placebo×100%.

3 | RESULTS

3.1 | Adolescent subgroup

In all, 1482 subjects were randomized in trial A, including 189 adolescents; 946 subjects were randomized in trial B, including 302 adolescents. The pooled adolescent FAS was comprised of 395 adolescents (N=201, 12 SQ HDM; N=194, placebo; see subject disposition in Figure 1). Slightly more subjects discontinued from the 12 SQ HDM group (n=27; 13%) than from the placebo group (n=19; 10%); the difference was explained by more AEs leading to discontinuation (n=11; 5% vs n=3; 2%).

Demographics and baseline characteristics for the pooled adolescent subpopulation are shown in Table 1. The treatment groups were well balanced. In addition to allergic rhinitis, about 20% of the adolescent subpopulation had a history of asthma. About half of the adolescent subpopulation were Asian and one-third were White. Most subjects (77%) were sensitized to allergens other than HDM; the three most common additional allergen sensitivities were grass pollen, cat dander and dog dander in trial A, and cedar, cypress and cat dander in trial B.

![FIGURE 1 Disposition of pooled adolescent subjects in the placebo group and the 12 SQ HDM group. [Colour figure can be viewed at wileyonlinelibrary.com]](image)
Efficacy assessments

In the pooled adolescent subpopulation, the average TCRS based on adjusted means was significantly improved with 12 SQ HDM vs placebo (treatment difference of −1.04; P < .01; Table 2), corresponding to a relative difference of 22% in favour of active treatment. The rhinitis DSS, rhinitis DMS and conjunctivitis DSS were significantly improved vs placebo (all P < .05; Table 2). There was a numerical improvement in the conjunctivitis DMS score (P = .06). Only 33% of subjects used conjunctivitis symptom-relieving medications during the efficacy assessment period.

The estimated probability of experiencing a rhinitis exacerbation day was 22.6% for placebo and 9.3% with 12 SQ HDM (OR = 0.35; 95% CI [0.14, 0.88]; P = .026). The estimated probability for experiencing a mild rhinitis day was 28.5% with placebo and 47.1% with 12 SQ HDM (OR = 2.23; 95% CI [1.18, 4.24]; P = .014). Assuming similar conditions, efficacy over 1 year may be estimated to 82 days with rhinitis exacerbation and 3½ months of mild days in the placebo group, compared with 34 days with rhinitis exacerbation and almost 6 months of mild days in the 12 SQ HDM group.

HDM-specific IgG₄ increased significantly in the 12 SQ HDM group following initiation of treatment (shown in Figure 2 for D. farinae-specific IgG₄) while no changes were observed in the placebo group. The between-group difference in change from baseline for active vs placebo was statistically significant from week 4 and onwards. At the end of trial, the between-group difference in log₁₀-transformed IgG₄ to D. farinae for the 12 SQ HDM group vs placebo group was 0.50 (SD 0.02), P < .01.

### Table 1
Demographics and baseline characteristics of the pooled adolescent subpopulation

|                | 12 SQ HDM (N=201) | Placebo (N=194) |
|----------------|-------------------|-----------------|
| Female, n (%)  | 81 (40%)          | 88 (45%)        |
| Mean age, y (SD)| 14.3 (1.6)        | 14.5 (1.7)      |
| Body mass index, kg/m² (SD) | 21.4 (4.8) | 21.5 (4.7) |
| Race           |                   |                 |
| Asian, n (%)   | 112 (56%)         | 106 (55%)       |
| White, n (%)   | 65 (32%)          | 70 (36%)        |
| Black or African American, n (%) | 12 (6%)   | 6 (3%)          |
| Multiracial, n (%) | 9 (4%)       | 11 (6%)         |
| American Indian or Alaska Native, n (%) | 3 (1%)       | 1 (<1%)         |
| Allergic history |                |                 |
| Subjects with allergic rhinitis, n (%) | 201 (100%) | 194 (100%)     |
| Mean duration of allergic rhinitis, y (SD) | 6.6 (3.6) | 7.1 (3.7)      |
| Subjects with concomitant asthma, n (%) | 39 (19%) | 40 (21%)       |
| IgE sensitization to HDM only, n (%) | 45 (22%) | 44 (23%)       |
| IgE sensitization to HDM and other allergens, n (%) | 156 (78%) | 149 (77%)     |
| Not sensitized to HDM, n (%) | - | 1 (<1%)     |
| Mean D. farinae serum specific IgE, kU/L (SD) | 1.17 (0.68) | 1.34 (0.57)  |
| Mean D. pteronyssinus serum specific IgE, kU/L (SD) | 1.13 (0.67) | 1.30 (0.62)  |

HDM, house dust mite; kU/L, kilo-units per litre; SD, standard deviation. *Protocol violation.

### Table 2
TCRS, DSS and DMS in the pooled adolescent subpopulation over the last 8 wk of treatment

| Adolescent subpopulation | 12 SQ HDM | Placebo | Treatment effect |
|--------------------------|-----------|---------|-----------------|
|                          | N | Score  | N | Score  | Absolute difference, (95% CI) | Relative difference | P-value |
| TCRS                     | 175 | 3.65   | 176 | 4.70   | −1.04 (−1.69; −0.40) | 22% | .01 |
| Rhinitis DSS             | 175 | 3.49   | 176 | 4.36   | −0.87 (−1.28; −1.46) | 20% | .01 |
| Rhinitis DMS             | 175 | 0.05   | 176 | 0.10   | −0.06 (0.00; −0.12) | 6% | .04 |
| Conjunctivitis DSS       | 175 | 0.82   | 176 | 1.10   | −0.28 (−0.03; 0.52) | 25% | .03 |
| Conjunctivitis DMS       | 175 | 0.02   | 176 | 0.05   | −0.03 (0.00; −0.05) | 6% | .06 |

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

*Adjusted mean values from linear mixed-effects model.

**Relative difference to placebo:** (placebo−12 SQ HDM)/placebo×100%.
3.3 | Safety

The safety profiles for the two complete trial populations have been previously described. Safety profiles for the two complete trial populations have been previously described.5,6 No new safety signals were identified in the adolescent subpopulation. More subjects in the active group reported treatment-related AEs; however, the majority were mild in intensity (Table 3). Less than 1% of the AEs reported by adolescent subjects were assessed as severe (7 events in the 12 SQ HDM group and 3 events in the placebo group). Two subjects treated with 12 SQ HDM reported 5 severe AEs that were assessed as treatment-related; the events were nausea, oral pruritus (2 events in 1 subject), tongue

pruritus and throat irritation. There were no treatment-related SAEs reported in the adolescent subpopulation and no severe local swellings and no adolescent subjects were treated with epinephrine due to AEs. One event of anaphylactic reaction was reported in the adolescent subpopulation; this concerned a 16-year-old male from the 12 SQ HDM group who experienced moderate throat swelling after consuming a cookie. The event occurred 2 days after discontinuation of treatment (on day 16 due to an AE of mouth ulceration) and was assessed as unrelated to treatment. The event was treated with diphenhydramine hydrochloride and resolved within 60 minutes.

### TABLE 3 Overall summary of AEs for adolescent subjects treated with placebo or 12 SQ HDM (safety set)

|                      | 12 SQ HDM (N=201) | Placebo (N=194) |
|----------------------|--------------------|-----------------|
|                      | Number of subjects with event (%) | Number of events (%) | Number of subjects with event (%) | Number of events (%) |
| All events           | 188 (94%)          | 1666 (100%)     | 157 (81%)          | 666 (100%)          |
| Causality            |                    |                 |                   |                   |
| Related              | 158 (79%)          | 1277 (77%)      | 64 (33%)          | 281 (42%)          |
| Not related          | 122 (61%)          | 381 (23%)       | 138 (71%)         | 372 (56%)          |
| Missing              | 2 (<1%)            | 8 (<1%)         | 3 (2%)            | 13 (2%)            |
| Severity             |                    |                 |                   |                   |
| Mild                 | 186 (93%)          | 1489 (89%)      | 151 (78%)         | 587 (88%)          |
| Moderate             | 39 (19%)           | 159 (10%)       | 39 (20%)          | 61 (9%)            |
| Severe               | 3 (1%)             | 7 (<1%)         | 3 (2%)            | 3 (<1%)            |
| Intensity of related AEs |                    |                 |                   |                   |
| Mild                 | 157 (78%)          | 1146 (85%)      | 62 (32%)          | 274 (91%)          |
| Moderate             | 23 (11%)           | 123 (13%)       | 5 (3%)            | 6 (7%)             |
| Severe               | 2 (<1%)            | 5 (<1%)         | -                 | -                 |
| SAEs                 |                    |                 |                   |                   |
| All SAEs             | -                  | -               | 2 (1%)            | 2 (<1%)            |
| Related SAEs         | -                  | -               | -                 | -                 |
| Action taken         |                    |                 |                   |                   |
| None                 | 185 (92%)          | 1573 (94%)      | 156 (80%)         | 624 (94%)          |
| Treatment interrupted| 26 (13%)           | 43 (3%)         | 15 (8%)           | 18 (3%)            |
| Treatment discontinued| 11 (5%)           | 31 (2%)         | 3 (2%)            | 3 (<1%)            |
| Not applicable       | 10 (5%)            | 11 (<1%)        | 10 (5%)           | 11 (2%)            |
| Missing              | 2 (<1%)            | 8 (<1%)         | 2 (1%)            | 10 (2%)            |
| Outcome              |                    |                 |                   |                   |
| Not recovered        | 7 (3%)             | 7 (<1%)         | 8 (4%)            | 14 (2%)            |
| Recovered            | 188 (94%)          | 1622 (97%)      | 155 (80%)         | 626 (94%)          |
| Recovered with sequelae| 14 (7%)          | 23 (1%)         | 14 (7%)           | 17 (3%)            |
| Recovering           | 9 (4%)             | 11 (<1%)        | 7 (4%)            | 8 (1%)             |
| Unknown              | 3 (1%)             | 3 (<1%)         | 1 (<1%)           | 1 (<1%)            |

AE, adverse event; N, number of subjects in safety set; SAEs, serious AEs, defined according to ICH Harmonised Tripartite Guideline E2A, Step 5.24 Note that solicited and unsolicited AEs were pooled for this summary.
Sublingual allergy immunotherapy with SQ HDM SLIT-tablet was clinically effective and well tolerated in adolescents with moderate-severe HDM allergic rhinitis. The efficacy and safety in the adolescent subpopulation appear to be comparable to the total trial population.

The improvement in the TCRS in adolescents is considered clinically relevant as defined by the World Allergy Organization definition and as predefined in the trial by Demoly et al. Significant improvements in rhinitis DSS, rhinitis DMS and conjunctivitis DSS were also observed with 12 SQ HDM treatment. Furthermore, the treatment reduced the patient’s probability for having rhinitis exacerbation days and increased the probability for having mild days with no more than minimal awareness of symptoms, parameters that are perhaps more tangible for patients to understand. The observed improvements are especially notable when considering all subjects, including those in the placebo group, were allowed to use allergy symptom-relieving medications throughout the trials. On that note, a meta-analysis of pharmacotherapies and SQ HDM SLIT-tablets found that nasal symptoms due to perennial allergens were only improved 3.7% with a leukotriene receptor antagonist, 4.8% with an oral antihistamine and 11.2% with an inhaled corticosteroid, whereas the SQ HDM SLIT-tablet improved nasal symptoms by 16.1%. Thus, the SQ HDM SLIT-tablet appears to provide clinically relevant benefits for adolescents with HDM allergy.

The current pooled results confirm the results of a phase 1 adolescent safety trial that determined the most common AEs with SQ HDM SLIT-tablet were oral pruritus and throat irritation. There is no difference between current pooled data and the phase 1 trial when observed events and their intensities were compared. However, many of the most common treatment-related AEs were reported at a higher incidence in the pooled analysis compared with the phase 1 trial, which is likely due to the use of solicited AEs in trial A. The side effect report card actively solicited the presence or absence of local AEs and resulted in higher proportions of subjects reporting specific AEs compared with previous SLIT-tablet trials. In contrast, the phase 1 adolescent trial and trial B used spontaneous AE reporting, resulting in similar AE reporting frequencies.

The efficacy results from this pooled analysis including subjects from North America and Japan are similar to a trial in European adults, where the difference in TCRS between 12 SQ HDM and placebo for the full analysis set was −1.22. Furthermore, the immunologic data are supportive of the observed clinical effect, and together, these data indicate that 12 SQ HDM is an effective treatment for various ages across geographically diverse regions. Specific IgG4 was significantly increased in the active group already after 4 weeks of treatment, suggesting that onset of efficacy in adolescents is comparable to that documented in adults (8-14 weeks).

Allergy immunotherapy is the only treatment modality with the capability to change the natural course of the allergic disease, thereby preventing its exacerbation and the possible progression from allergic rhinitis to asthma symptoms. Further, not well-controlled allergic rhinitis reduces sleep quality impairing concentration, school attendance and performance, highlighting the importance of treating allergic rhinitis effectively in adolescents.

A limitation of the current analyses is that the inclusion criteria for the two trials differed in relation to requirements of a higher level of serum specific IgE and a positive nasal provocation test in trial B. This could lead to a more sensitive population as data with grass sublingual immunotherapy have suggested a trend towards higher efficacy in subjects with higher pre-treatment specific IgE levels. In addition, the analyses were performed post hoc and as such should be interpreted with caution. More information on the efficacy of allergy immunotherapy in children and adolescents with HDM allergic asthma and HDM allergic rhinitis would be of interest.

In conclusion, this post hoc analysis suggests that sublingual allergy immunotherapy with the SQ HDM SLIT-tablet (12 SQ HDM dose) is effective with a clinically relevant magnitude of effect, and well tolerated in adolescents with moderate-severe HDM allergic rhinitis.
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CONFLICT OF INTEREST

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