

Article type : Original

TITLE PAGE

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

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Running title: SQ HDM SLIT-tablet for adolescents

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12747
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Online repository: NA

ABSTRACT PAGE

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Journal: PAI

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 2 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 one year of treatment. The primary endpoint in both trials was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment in the active group compared to 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 versus 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 versus placebo in the pooled adolescent subpopulation (all $p < 0.05$).

There were no new safety signals for adolescents. The frequency of adverse events were 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

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Introduction

Allergic rhinitis is estimated to affect 17–29% of the population across Europe (1) 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 (2). Allergy to house dust mite (HDM) is prevalent in children and adolescents and has notable clinical implications (3). Allergy immunotherapy is the only treatment for allergies that can alter the underlying pathologic disease mechanisms. Yet, HDM allergy immunotherapy for allergic respiratory diseases (i.e. 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 (4).

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 (4).

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 (5-11). One safety trial conducted in adolescents found that SQ HDM SLIT-tablets were well-tolerated (12). 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 to 17 years) (5;6). 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.

Methods

Trial designs

Two randomized, parallel-group, double-blind, placebo-controlled, multi-site, 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 one trial was conducted in Japan (Trial B; JapicCTI number 121848). Both trials have been previously described (5;6). The trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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 pharmacological 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 1 symptom being severe on 5 of 7 consecutive days) before randomisation when subjects were expected to have natural exposure to HDM and when allergy-relieving medications were withdrawn. Subjects were randomised between November and March, except from 109 subjects whom were randomized based on a positive HDM chamber challenge test. Subjects with $FEV_1 < 80\%$ 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 randomised between September and November.

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) (13).

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.

Assessments

The primary endpoint 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 to 24 points. The rhinitis DSS was the sum of 4 nasal symptoms (runny nose, blocked nose, sneezing, itchy nose), each rated on a scale from 0 (no symptoms) to 3 (severe symptoms) with a range of 0 to 12 points. The rhinitis DMS consisted of symptomatic medication scores with a range of 0 to 12. Secondary endpoints were rhinitis DSS, conjunctivitis DSS (sum of gritty feeling/red/itchy eyes and watery eyes) rated on a scale of 0 to 3, rhinitis DMS, and conjunctivitis DMS (range of 0 to 8). Details of symptom and medication scoring have been previously described (5;6). Rhinitis exacerbation days were defined as days with an allergic rhinitis symptom score of 6, or 5 with one individual symptom scored 3 (i.e. implying a symptom that was hard to tolerate and caused interference with activities of daily living and/or sleeping). Mild days were defined as days with no individual symptom scored higher than 1 (i.e. 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 IgG₄ 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 (14). AEs in trial B were assessed by general questioning during site visits.

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 two 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 endpoint was Hodges-Lehmann estimate with 95% confidence intervals (i.e. based on the median TCRS) while in trial B the primary efficacy endpoint 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. Percent relative treatment difference versus placebo was calculated as (placebo–12 SQ-HDM)/placebo x 100%.

Results

Adolescent subgroup

In all, 1482 subjects were randomised 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% versus 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 sensitised to allergens other than HDM, the 3 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.

Efficacy assessments

In the pooled adolescent subpopulation, the average TCRS based on adjusted means was significantly improved with 12 SQ-HDM versus placebo (treatment difference of -1.04 ; $p < 0.01$; **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 versus placebo (all $p < 0.05$; **Table 2**). There was a numerical improvement in the conjunctivitis DMS score ($p = 0.06$). 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]; $p = 0.026$). 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]; $p = 0.014$). 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 versus placebo were 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 versus placebo group was 0.50 (SD 0.02), p<0.01.

Safety

The 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, 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.

The most common treatment-related AEs were oral pruritus (reported by 45% of subjects in the active group vs. 8% in placebo), throat irritation (40% vs. 19%), and ear pruritus (27% vs. 6%) (Table 4).

Discussion

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 appears to be comparable to the total trial population (5;6).

The improvement in the TCRS in adolescents is considered clinically relevant as defined by the World Allergy Organization definition (15) and as predefined in the trial by Demoly et al (7). 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% (16). 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 (12). 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 (17;18). 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 (5). 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 (7). Furthermore, the immunologic data is 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) (7;10).

Allergy specific immunotherapy is the only treatment modality with the capability to change the natural course of the allergic disease, thereby preventing its exacerbation (19) and the possible progression from allergic rhinitis to asthma symptoms (20;21). Further, not well-controlled allergic rhinitis reduces sleep quality impairing concentration, school attendance and performance (22), highlighting the importance of treating allergic rhinitis effectively in adolescents.

A limitation of the current analyses is that the inclusion criteria for the 2 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 has suggested a trend towards higher efficacy in subjects with higher pre-treatment specific IgE levels (23). Additionally, the analyses were performed post hoc and as such should be interpreted with caution. More information on the efficacy of allergy specific 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.

Acknowledgments

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA and Torii Pharmaceutical Co., Ltd., Tokyo, Japan. In this context the authors thank all the involved investigators for their participation, and the clinical trial teams for clinical project management, operational oversight, quality control, safety monitoring, data management, and statistics. Medical writing and editorial assistance was provided by Erin P. Scott, PhD, Scott Medical Communications, LLC, Frisco, TX, US; and Bente Riis, PhD, ALK, Hørsholm, Denmark. This assistance was funded by ALK, Hørsholm, Denmark.

Funding source: Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA and Torii Pharmaceutical Co., Ltd., Tokyo, Japan. Medical writing assistance was funded by ALK, Hørsholm, Denmark.

Conflict of interest: T. Matsuoka has received grants from Torii Pharmaceutical Co. Ltd., MSD and Mitsubishi Tanabe Pharma, and received lecture fees from Torii Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma and Taiho Pharma. D.I. Bernstein has served as a consultant for Merck & Co., Inc., Circassia, Teva, ProctorGamble, Sanofi Aventis, and Stallergenes Greer, received grants from Merck & Co., Inc., Circassia, Stallergenes Greer, Teva, GlaxoSmithKline, Pfizer, Amgen, Pearl, Genentech, Allergy Thempy, Boehringer Ingelheim, and AstraZeneca, and received lecture fees from Merck & Co., Inc., and AstraZeneca. K. Masuyama has received consultancy fees from Torii Pharmaceutical Co.,Ltd, and Shionogi & Co., Ltd. H. Nolte is employed by ALK, Hørsholm, Denmark (but was, while Trial A was ongoing, employed by Merck & Co., Inc., Kenilworth, NJ, USA). K. Okamiya is employed by Torii Pharmaceutical Co., Ltd., Tokyo, Japan. D. Seitzberg is employed by ALK, Hørsholm, Denmark. H.S. Nelson has served as a consultant for Merck & Co., Inc., and Circassia, and received grants from Circassia.

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

	12 SQ-HDM	Placebo
	(N=201)	(N=194)
Female, n (%)	81 (40%)	88 (45%)
Mean age, years (SD)	14.3 (1.6)	14.5 (1.7)
Body mass index, kg/m ² , (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%)
Multi-Racial, 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, years (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 sensitisation to HDM and other allergens, n (%)	156 (78%)	149 (77%)
Not sensitised to HDM [†] , n (%)	-	1 (<1%)
Mean <i>D. farinae</i> serum specific IgE, kU/L (SD)	1.17 (0.68)	1.34 (0.57)
Mean <i>D. pteronyssinus</i> serum specific IgE, kU/L (SD)	1.13 (0.67)	1.30 (0.62)

[†]: protocol violation; HDM: house dust mite; kU/L: kilo-units per litre; SD: standard deviation

Table 2. TCRS, DSS and DMS in the pooled adolescent subpopulation over the last 8 weeks 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%	<0.01
Rhinitis DSS	175	3.49	176	4.36	−0.87 (−0.28; −1.46)	20%	<0.01
Rhinitis DMS	175	0.05	176	0.10	−0.06 (0.00; −0.12)	60%	0.04
Conjunctivitis DSS	175	0.82	176	1.10	−0.28 (−0.03; 0.52)	25%	0.03
Conjunctivitis DMS	175	0.02	176	0.05	−0.03 (0.00; −0.05)	60%	0.06

[#]: Adjusted mean values from linear mixed-effects model; *: Relative difference to placebo: (placebo−12 SQ-HDM)/placebo x 100%;

DMS: daily medication score; DSS: daily symptom score; TCRS: total combined rhinitis score

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

Table 4. Summary by SOC and PT of the most frequent treatment-related AEs (≥5% of subjects in the 12 SQ-HDM group) (safety set)

SOC	12 SQ-HDM (N=201)	Placebo(N=194)
PT	n (%) e	n (%) e
Ear and labyrinth disorders		
Ear pruritus	54 (27%) 167	11 (6%) 40
Gastrointestinal disorders		
Abdominal pain upper	18 (9%) 55	13 (7%) 17
Glossodynia	22 (11%) 71	4 (2%) 13
Lip swelling	20 (10%) 41	1 (<1%) 1
Mouth swelling	20 (10%) 29	2 (1%) 4
Nausea	17 (8%) 54	8 (4%) 14
Oral pruritus	91 (45%) 276	15 (8%) 25
Palatal swelling	10 (5%) 23	1 (<1%) 1
Paraesthesia oral	18 (9%) 37	-

Swollen tongue	19 (9%) 32	3 (2%) 4
Tongue ulceration [#]	14 (7%) 28	3 (2%) 5
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal discomfort	12 (6%) 12	-
Pharyngeal oedema	17 (8%) 32	6 (3%) 9
Throat irritation	80 (40%) 248	36 (19%) 94

[#]: A cognitive debriefing study suggested that subjects might have misinterpreted the solicited question (have you experienced tongue ulcer/sore on the tongue) as tongue pain rather than an actual ulcer (5); e: number of events;

N: number of subjects in safety set, n: number of subjects with event, %n: percentage of subjects in safety set with the event; PT: preferred term; SOC: system organ class.

Note that solicited and unsolicited AEs were pooled for this summary

Figure legends

Figure 1: Disposition of pooled adolescent subjects in the placebo group and the 12 SQ-HDM group

Figure 2. Change from baseline in log10-transformed *D. farinae* IgG₄

Figure 1: Disposition of pooled adolescent subjects in the placebo group and the 12 SQ-HDM group

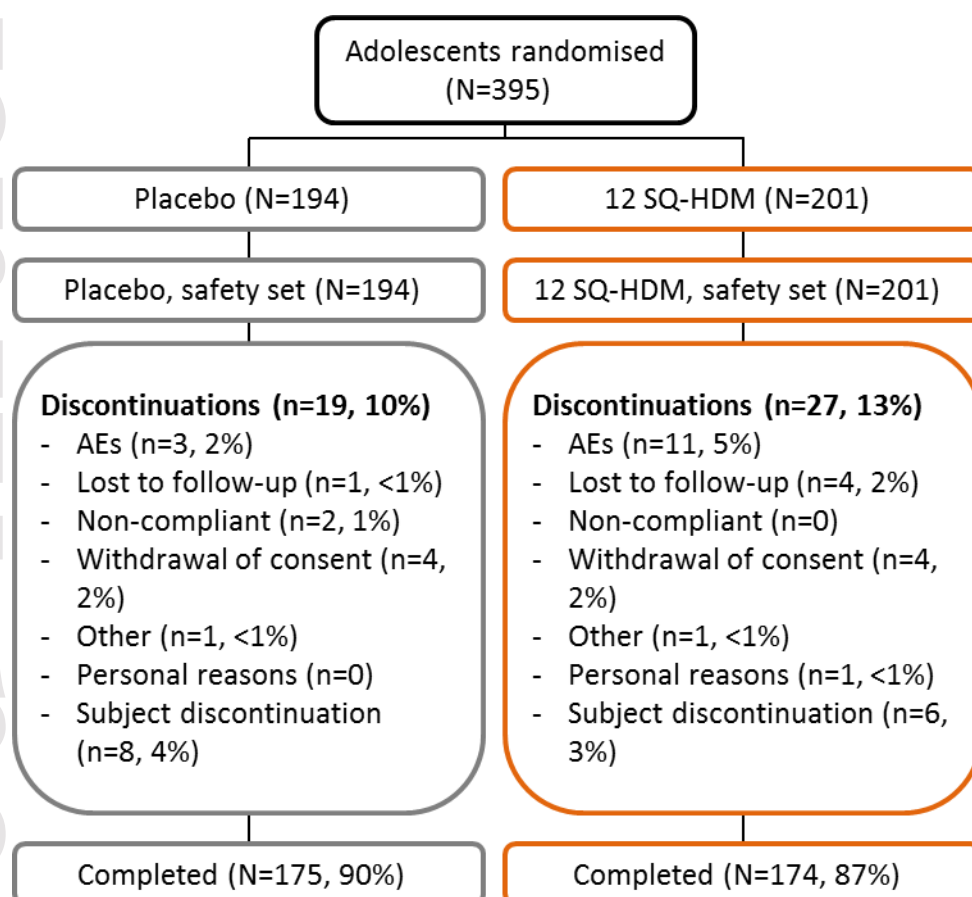


Figure 2. Change from baseline in log10-transformed *D. farinae* IgG₄

