

SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms



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ABSTRACT

Background: House dust mite (HDM) allergy is associated with persistent allergic rhinitis (AR) and allergic asthma.

Objective: To investigate the efficacy and safety of a SQ HDM sublingually administered immunotherapy tablet (ALK, Hørsholm, Denmark) in adults and adolescents with HDM respiratory allergic disease and report the AR results.

Methods: Six hundred four subjects at least 14 years old with HDM AR and mild to moderate HDM allergic asthma were randomized 1:1:1:1 to double-blinded daily treatment with 1, 3, 6 SQ-HDM or placebo. End-of-treatment rhinoconjunctivitis symptoms and medication score were predefined extrapulmonary end points. A subgroup analysis was conducted post hoc in subjects with a total combined rhinitis score (TCRS) > 0 (ie, with AR symptoms and/or AR medication use during the 4-week baseline period). The subgroup was comprised of 498 subjects (82%).

Results: In the subgroup, the absolute difference in end-of-treatment TCRS between 6 SQ-HDM and placebo was −0.78 (95% confidence interval −1.47 to −0.07, relative difference 28.8%, $P = .0357$). Furthermore, a significant difference was found for the total score of the Rhinitis Quality of Life Questionnaire with Standardized Activities RQLQ(S) and for the individual domains: activities, sleep, non-nose and non-eye symptoms, and nasal symptoms. For the TCRS and Rhinitis Quality of Life Questionnaire score, a dose response was seen, with numerically lower, nonsignificant differences for 1 and 3 SQ-HDM. The predefined analysis for the entire trial population showed no statistically significant difference between the placebo and actively treated groups. No safety concerns were observed.

Conclusion: Efficacy in mild to severe AR of 6 SQ-HDM compared with placebo was demonstrated by statistically significant improvements in TCRS and Rhinitis Quality of Life Questionnaire score in subjects with AR present at baseline. The treatment was well tolerated.

Trial Registration: EudraCT, no 2006-001795-20; ClinicalTrials.gov, identifier NCT00389363.

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Funding: The trial was sponsored by ALK (Hørsholm, Denmark) who assumes overall responsibility for the trial and was involved in the trial design and conduct.

Introduction

Patients with house dust mite (HDM) respiratory allergic disease can have symptoms from both the upper (allergic rhinitis [AR]) and lower (allergic asthma [AA]) respiratory tract. Nearly all patients with AA and HDM sensitization have AR, and approximately half the patients with AR and HDM sensitization have asthma.¹ Allergy immunotherapy targets the underlying allergic disease and thus could have beneficial effects on clinical symptoms manifesting as AA, AR or both.²

The safety and efficacy of the SQ HDM sublingually administered immunotherapy (SLIT) tablet (ALK, Hørsholm, Denmark) in mild to moderate HDM AA has recently been described.³ This randomized, double-blinded, placebo-controlled phase II/III trial confirmed efficacy in mild to moderate AA of 6 SQ-HDM compared with placebo and the treatment could reduce the inhaled corticosteroid (ICS) dose required to maintain asthma control. The primary analysis revealed a mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS dose of 81 mg ($P = .004$). Relative mean and median reductions were 42% and 50% for 6 SQ-HDM and 15% and 25% for placebo.³

Allergic rhinoconjunctivitis was assessed as a secondary objective in this trial, and eligibility required a history of HDM AR and HDM AA and a positive test of sensitization. A proportion of the trial subjects reported no rhinitis symptoms and no use of pharmacotherapy for AR during the entire 4-week baseline period. The remaining subjects (82% of entire trial population) had a non-zero total combined rhinitis score (TCRS; ie, sum of AR daily symptoms score and daily AR medication score averaged over 4-week baseline period). The effect of the SQ HDM SLIT-tablet in this subgroup of subjects with symptoms from HDM AR at any time during the 4-week baseline period before randomization was investigated post hoc.

Quality of life in patients with HDM allergy may be impaired by a high level of nasal symptoms associated with impaired sleep caused by symptoms such as a blocked nose,^{4,5} whereas eye symptoms less frequently affect sleep and quality of life in patients with HDM allergy.^{6,7} Hence, nasal symptoms seem to be the predominant and clinically most relevant extrapulmonary manifestation of HDM allergy. For this reason, the subgroup analysis is focused on AR.

The trial was sponsored by ALK.

Methods

The methods described herein are pertinent to the AR results. A detailed description of the trial and the results related to asthma have been published.³

Trial Design

This was a multisite, multiple-dose, randomized, double-blinded, parallel-group, placebo-controlled trial performed at 81 sites in Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, and Poland. The trial design is presented in Figure 1.

Subjects were randomized (1:1:1:1) to double-blinded treatment with 1, 3, or 6 SQ-HDM or placebo as 1 daily tablet administered sublingually. Subjects received intervention treatment for approximately 12 months.

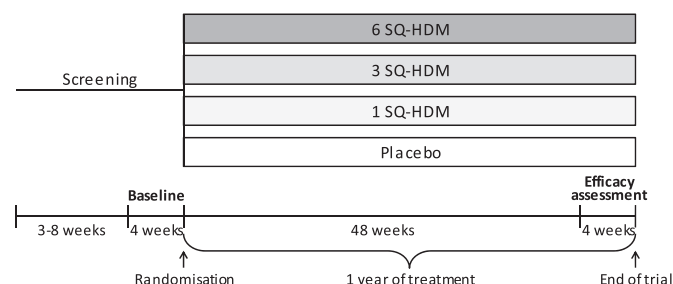


Figure 1. Trial design depicts the 4-week periods when assessments of allergic rhinitis symptoms and medication use are equivalent to the inhaled corticosteroid stable periods used for assessing the allergic asthma end point.³

Trial Population

The trial population was comprised of subjects at least 14 years of age with controlled asthma (as defined by the Asthma Control Questionnaire⁸), mild to moderate HDM AA requiring ICS use (100–800 μ g/day of budesonide or equivalent), a clinical history of HDM AR, a positive skin prick test (wheal diameter ≥ 3 mm), and specific IgE (≥ 0.70 kU/L) to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*. The population was characterized by assessing demographic parameters and disease-specific parameters, such as sensitization pattern, disease severity, and comorbidities. The subgroup consisted of 82% of the entire trial population who reported AR symptoms and/or medication use, demonstrated as a TCRS > 0 , during the 4-week baseline period.

Intervention Medication

The tablets (active and placebo) were manufactured and provided by the sponsor and were oral lyophilisates containing standardized extracts of *D pteronyssinus* and *D farinae* in a 1:1 ratio or a placebo that was similar in appearance, smell, and taste. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. In previous publications (abstracts and phase I publication⁹), the units were designated in development units. One development unit corresponds to 1 SQ-HDM. The sponsor provided ICS and rescue medication to relieve asthma and rhinoconjunctivitis symptoms.

Randomization

Randomization was performed according to the sponsor-generated allocation schedule by a trial-independent statistician.³

End Points and Assessments

The prespecified extrapulmonary end points for the entire trial population comprised rhinoconjunctivitis symptoms and medication scores and Rhinitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) scores.¹⁰ The end points analyzed in the post hoc analysis of the subgroup with AR at baseline comprised the TCRS, AR symptoms, AR medication, the RQLQ(S), and the individual RQLQ(S) domains. The composite end point, TCRS, was the sum of the daily AR symptoms and daily AR medication score averaged over the 4-week end-of-trial efficacy assessment period. The range of the score was 0 to 24, as detailed below.

Symptoms during the past 24 hours were evaluated by the subjects in an electronic diary by scoring 4 nose symptoms (runny nose, sneezing, itchy nose, and blocked nose) and 2 eye symptoms (watery eyes and gritty feeling/red/itchy eyes) on a scale of 0 to 3 (no symptoms, mild symptoms, moderate symptoms, and severe symptoms). For the subgroup analysis, omission of eye symptoms led to a maximum daily AR symptom score of 12.

Additional pharmacotherapy against allergic symptoms was standardized and taken in the form of desloratadine tablets at a maximum of 5 mg daily, 32 μ g of budesonide nasal spray at a maximum of 2 puffs per nostril daily, and 5 mg of prednisone in the event of exacerbations. Subjects were instructed to take these medications only when needed for control of their symptoms. Once symptoms were alleviated, the subject had to stop taking pharmacotherapy. The use of pharmacotherapy was recorded in the daily diary and the medication scoring scale was not disclosed to the trial subjects. Oral prednisone was used by only a few subjects and it had no influence on the AR end point and thus was omitted from the assessment of the AR medication score. Desloratadine had a score of 4 (for 5 mg) and budesonide had a score of 8 (2 per puff), leading to a maximum daily AR medication score of 12.

The RQLQ(S) is comprised of 28 items in 7 domains, with each scored on a 7-point scale (0, no impairment; 6, maximum

impairment). Subjects were to respond to each item after recalling their experience during the past week. The 7 domains were activities, sleep, non-nose and non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.¹⁰ Overall scores and domain scores were calculated for each subject at randomization/initiation of treatment (visit 4, baseline) and at the end-of-trial visit (visit 12).

Symptoms, medication use, and RQLQ(S) were recorded daily by subjects in an electronic diary during 4 weeks prior to randomization (baseline) and again after 1 year of treatment during the efficacy assessment, which took place over a period of 4 weeks before the trial ended (Fig 1). The 4 weeks before randomization (baseline period) and the 4 weeks at the end of treatment (efficacy assessment period) are equivalent to the ICS stable periods for the assessment of asthma end points.³

Statistical Methodology

The efficacy end point of the post hoc subgroup analysis was the average TCRS during the efficacy evaluation period. The end point was analyzed using a linear mixed-effects model based on non-missing observations of the population (subgroup with TCRS >0 during baseline). The square root of the average TCRS was the response variable, treatment was a fixed class effect, the square root of the average TCRS during baseline was a regression variable, and country was a random class variable. The different residual error for each treatment group was specified in the linear mixed-effects model. The linear mixed-effects model was estimated using the method of restricted maximum likelihood. Denominator degrees of freedom were calculated using the Kenward-Roger approximation. Parameter estimates, back-transformed adjusted means, and differences in back-transformed adjusted means were calculated together with the SE. The difference in the back-transformed adjusted means was calculated together with the associated *P* value and 95% confidence intervals.

The RQLQ(S) overall and domain scores were analyzed at the end of the trial similarly to the primary end point,³ with a linear mixed model including treatment group and baseline value as fixed effects and center as random effect, as described in the eMethods. A description of the statistics for the predefined extrapolatory analyses for the entire trial population is available in the eMethods.

Ethics

The trial is identified by EudraCT number 2006-001795-20 and clinicaltrials.gov identifier NCT00389363. The trial was designed, approved, consented to, and conducted according to the principles of Good Clinical Practice by the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use.¹¹ This included the collection of written informed consent from all trial subjects before the initiation of any trial-related procedures.

Results

Trial Population

The entire trial population consisted of 604 randomized subjects described in the primary publication.³ Of the entire trial population, 489 randomized subjects (82%) had a TCRS > 0 during baseline. Eight-nine percent of this subgroup completed the trial, evenly distributed across treatment groups. The rate of adverse event (AE) discontinuations was numerically slightly higher for 3 SQ-HDM than for the other treatment groups, which also was the case for the entire trial population.³

The subject disposition for this subgroup with a TCRS > 0 during baseline is presented in Table 1.

Half the subjects were male, 98% were white, baseline body measurements were within normal ranges, 83% were polysensitized, and 6% were adolescents. Demographic and baseline characteristics are presented in Figure 2.

Efficacy in Rhinitis

The efficacy data representing the subgroup with a TCRS > 0 during baseline are presented in Figure 3, depicted as dose-response curves. Values for medians and raw means are listed in the panel section of Figure 3.

The statistical analysis of TCRS is presented in Table 2 in addition to the analysis of the overall RQLQ(S) results for the subgroup.

A dose response was observed for the TCRS, with the most pronounced effect in the 2 highest dose groups, and with the difference from placebo being statistically significant only for 6 SQ-HDM. For RQLQ(S), the difference between 6 SQ-HDM and placebo also was statistically significant, whereas the lower dose groups yielded numerically smaller and nonsignificant effects.

For the individual components of the TCRS, the mean values of symptoms score during baseline and at the end of treatment were 1.56 and 1.24 for 1 SQ-HDM, 1.75 and 1.14 for 3 SQ DHM, 1.54 and 1.10 for 6 SQ-HDM, and 1.69 and 1.49 for placebo. The mean values for medication scores were 2.80 and 2.11 for 1 SQ-HDM, 3.27 and 2.22 for 3 SQ DHM, 2.92 and 2.14 for 6 SQ-HDM, and 2.89 and 2.61 for placebo.

The adjusted mean values at the end of treatment for 6 SQ-HDM and placebo for the individual components of the TCRS (Fig 4) showed that all individual scores were numerically lower for 6 SQ-HDM than for placebo, with statistically significant differences between the 2 groups for 3 of the 4 individual nose symptom domains (runny nose, *P* = .0086; blocked nose, *P* = .0176; sneezing, *P* = .0254; itchy nose, *P* = .0975). In addition to the RQLQ(S), the individual domains of the RQLQ(S) were analyzed. The results are shown in Figure 4 and showed statistically significant differences between 6 SQ-HDM and placebo for activities (*P* = .0463), sleep (*P* = .0002), non-nose and non-eye symptoms (*P* = .0062), and nasal symptoms (*P* = .0371).

Table 1

Subject disposition in subgroup with TCRS > 0 during baseline^a

	Placebo, n (%)	1 SQ-HDM, n (%)	3 SQ-HDM, n (%)	6 SQ-HDM, n (%)	Active all, n (%)	Overall, n (%)
Randomized	107 (100)	117 (100)	131 (100)	134 (100)	382 (100)	489 (100)
Withdrawn	69 (12)	11 (9)	20 (15)	14 (10)	45 (12)	56 (11)
Withdrawal of consent	2 (2)	2 (2)	6 (5)	2 (1)	10 (3)	12 (2)
Pregnancy	2 (2)	1 (<1)	2 (2)	2 (2)	3 (<1)	5 (1)
Lost to follow-up	3 (3)	1 (<1)	1 (<1)	3 (2)	5 (1)	8 (2)
Noncompliance	1 (<1)	3 (3)	2 (2)	4 (3)	9 (2)	10 (2)
Adverse event	1 (<1)	2 (2)	7 (5)	4 (3)	13 (3)	14 (3)
Other	2 (2)	2 (2)	2 (2)	1 (<1)	5 (1)	7 (1)
Completed	96 (90)	77 (66)	111 (85)	120 (90)	337 (88)	433 (89)

Abbreviation: TCRS, total combined rhinitis score.

^aAll randomized subjects were treated with the investigational medicinal product.

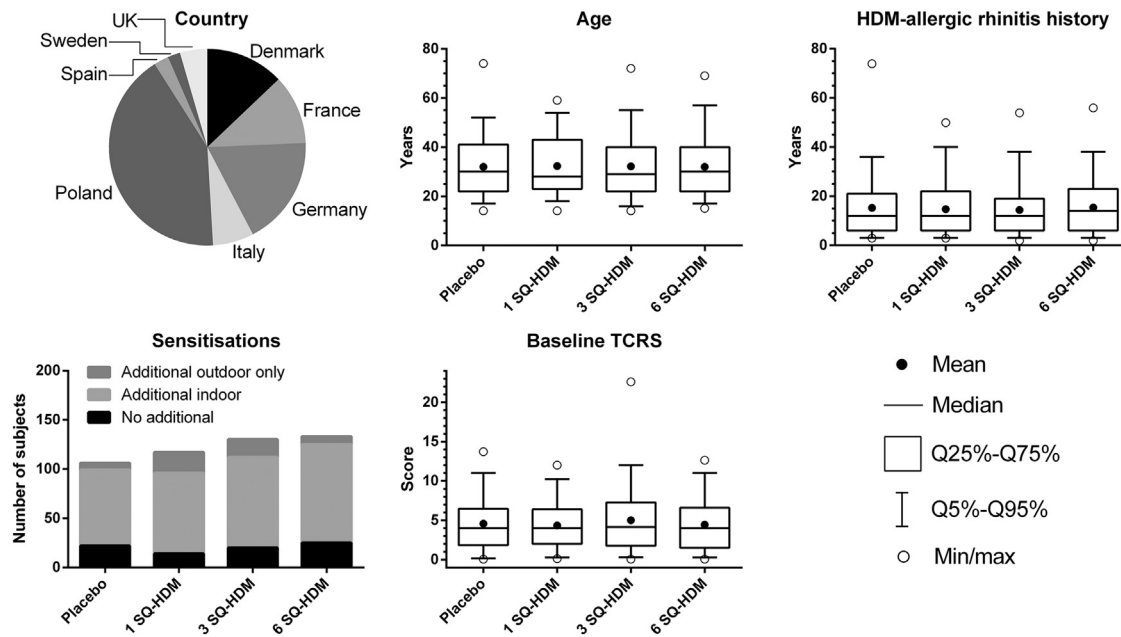


Figure 2. Demographic and baseline characteristics of subgroup with a TCRS > 0 during baseline. Age and HDM allergic rhinitis history were assessed at screening. Additional sensitizations were any sensitizations apart from *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*, as assessed by skin prick testing at screening. *Additional indoor* refers to at least 1 other indoor allergen (animal hair and dander, molds). *Additional outdoor only* refers to no other indoor allergens but at least 1 outdoor allergen. HDM, house dust mite; TCRS, total combined rhinitis score.

Analysis of the predefined extrapulmonary end points for the entire trial population (ie, including subjects with previous AR, but no AR symptoms or medication during the baseline period) did not show a statistically significant difference between active treatment and placebo; results and conclusions for this are available in the [eMethods](#).

A significantly larger proportion of subjects with a TCRS = 0 during baseline used a daily ICS dose > 400 µg budesonide at baseline compared with subjects using a daily dose of ICS ≤ 400 µg at

baseline (23% and 16%, respectively). This difference was statistically significant ($P = .0301$; see [eMethods](#)).

Safety

The AEs are reported as Medical Dictionary for Regulatory Activities preferred terms. This section concerns only AEs occurring after randomization in the subgroup with a baseline TCRS > 0. The data are presented in [Table 3](#). Overall, the reporting pattern was

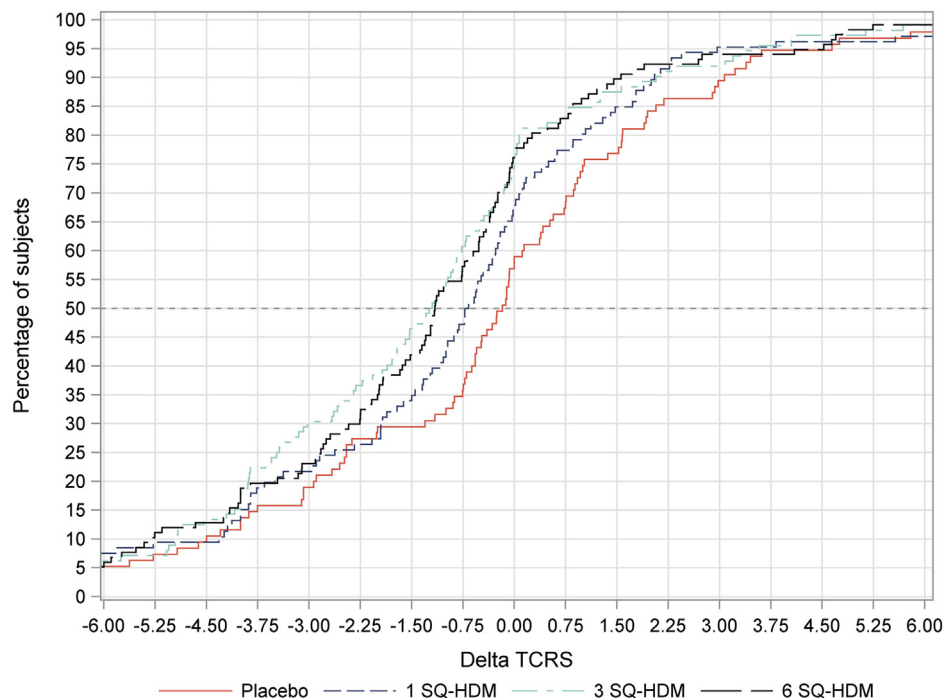


Figure 3. Empirical cumulative distribution of the change in TCRS from baseline to end of treatment for all treatment and placebo groups. The panel section lists medians, raw means, and SDs for individual treatment groups. TCRS, total combined rhinitis score.

Table 2

Statistical analyses of TCRS and RQLQ(S) in the subgroup with a TCRS higher than 0 comparing the 3 dose groups with placebo

	n	Adjusted mean	Difference from placebo		
			Absolute (95% CI)	Relative, %	P value
TCRS					
6 SQ-HDM	117	1.93	−0.78 (−1.52 to −0.04)	28.8	.036
3 SQ-HDM	112	2.01	−0.70 (−1.45 to 0.04)	26.0	.063
1 SQ-HDM	106	2.24	−0.47 (−1.24 to 0.30)	17.4	.23
Placebo	95	2.71			
RQLQ(S)					
6 SQ-HDM	119	0.80	−0.24 (−0.43 to −0.05)		.012
3 SQ-HDM	112	0.89	−0.15 (−0.34 to 0.04)		.11
1 SQ-HDM	104	0.89	−0.15 (−0.35 to 0.04)		.13
Placebo	96	1.04			

Abbreviations: CI, confidence interval; RQLQ(S), Rhinitis Quality of Life Questionnaire with Standardized Activities; TCRS, total combined rhinitis score.

distributed in 2 groups, with lower rates for placebo and 1 SQ-HDM than for 3 and 6 SQ-HDM. The most frequent AEs were oral pruritus, upper respiratory tract infections, and asthma, with upper respiratory tract infections being reported with similar frequency in the active treatment and placebo groups and oral pruritus and asthma reported more frequently in the active treatment groups than in the placebo group. All these reactions were mild or moderate in intensity. For most subjects, the occurrence of local allergic reactions after tablet administration abated within weeks to a few months. For all 4 treatment groups, most asthma exacerbations that were observed during the trial occurred during the ICS adjustment periods. Twenty-nine severe AEs were reported, with the highest rate observed for 3 SQ-HDM. Two serious AEs were assessed by the authors and the sponsor as related to the intervention: a case of dizziness in the 3 SQ-HDM group and a case of migraine in the 1 SQ-HDM group. Four severe AEs were assessed as related to the treatment, and 2 of these were serious AE and were described earlier. The remaining 2 cases were pruritus and facial edema. The subject with pruritus developed symptoms 23 days after the first intake of the intervention medication. The subject received oral antihistamines and the symptoms resolved after 9 days. There were no changes to the intervention medication. The subject with facial edema developed symptoms 65 days after the first intake of the intervention medication. The symptoms resolved within 1 day, and the subject did not receive any treatment. The subject discontinued the trial after this event. In total, 14 subjects (3%) discontinued the trial prematurely because of an AE, with the highest rates observed for 3 and 6 SQ-HDM (5% and 3%, respectively). No systemic allergic reactions were reported, and no subjects required treatment with

epinephrine. The safety results for this subpopulation are overall comparable to the safety results for the entire trial population.³

Discussion

A treatment effect of −0.78 (95% confidence interval −1.47 to −0.07) in TCRS was found for 6 SQ-HDM compared with placebo, with the relative difference being 28.8%. The results are comparable to what was found in a recently reported trial, although the scoring scales differ between the 2 trials, preventing direct comparisons. That trial assessed the efficacy and safety of 2 doses of a different HDM SLIT-tablet over 1 year in 509 subjects with moderate to severe HDM-induced AR.¹² After 1 year of treatment, the 2 active doses significantly improved the primary end point of Average Adjusted Symptom Score (a total symptom score adjusted for rescue medication use) by 17.9% and 20.2%, respectively, compared with placebo. In contrast to the present study, there did not appear to be a significant dose-dependent effect for efficacy.¹² Taken together, these 2 trials with different products support the HDM SLIT-tablet concept in AR.

SLIT-tablet therapy has also been shown to be effective in pollen allergy-related symptoms.^{13–19} A direct comparison of HDM SLIT-tablet with pollen SLIT-tablet trials is made difficult by the fact that symptom and medication scoring scales differ between trials, especially because conjunctivitis symptoms are more prominent in pollen allergy. However, overall, the measured relative treatment effect in the present trial is within range of what has been seen in pollen SLIT-tablet trials.^{13–19} The present results suggest a dose-response trend, with the highest and only statistically significant effect compared with placebo observed for 6 SQ-HDM. This could be a power issue, because this is a subgroup analysis and the trial was not powered for analysis of AR but for an analysis of ICS reduction. However, the results most likely imply that 1 and 3 SQ-HDM are below the effective dose range for most patients. This is in accord with the results for the asthma end points.³

In the post hoc analysis, the clinical effect of 6 SQ-HDM was supported by a statistically significant improvement of quality of life as assessed with the RQLQ(S) instrument. In particular, nasal symptoms and sleep improved, and, interestingly, the difference in scores was largest for blocked nose of the 4 individual nasal symptom components of the TCRS. The literature suggests a link between AR, impaired sleep, and decreased quality of life. Pathophysiologic mechanisms can be ascribed to increased exposure to mite allergen when in bed, circadian fluctuations, and/or nighttime decreases in cortisol levels that affect inflammatory cytokines and other mediators.^{20–22} Sleep disruption is frequent in patients with AR^{4,5,23} and is believed to be strongly associated to nasal congestion,^{4,24,25} leading

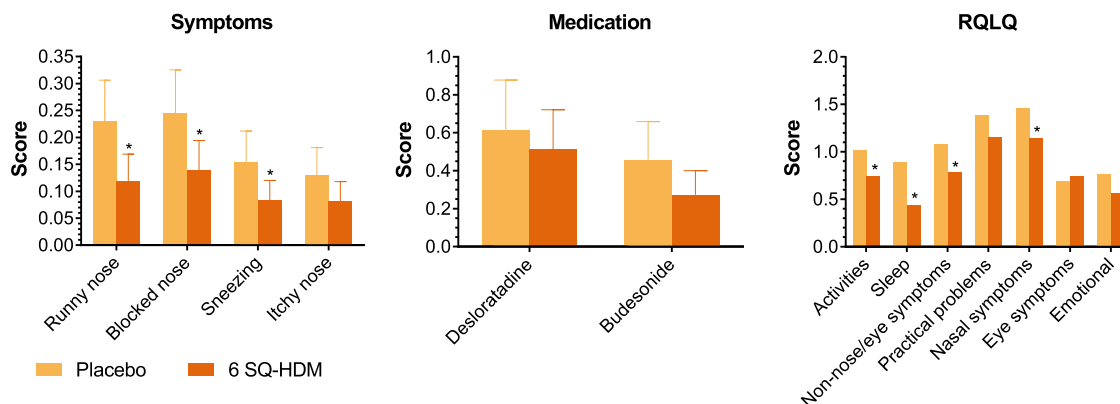


Figure 4. End-of-treatment scores for individual components of the total combined rhinitis score (nasal symptoms and medication) and RQLQ(S) in the placebo group (yellow) and the 6 SQ-HDM group (orange) for the subgroup of subjects with TCRS > during baseline. The scores are shown as adjusted means with 95% confidence intervals. Asterisks designate statistically significant differences between placebo and 6 SQ-HDM. RQLQ, Rhinitis Quality of Life Questionnaire with Standardized Activities.

Table 3Summary of adverse events occurring after first tablet intake in subgroup with TCRS > during baseline^a

	Placebo (n = 107)		1 SQ-HDM (n = 117)		3 SQ-HDM (n = 131)		6 SQ-HDM (n = 134)		Active all (n = 382)		Overall (n = 489)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
All AEs	61 (57)	152	64 (55)	177	88 (67)	299	88 (66)	297	240 (63)	775	301 (62)	925
Causality												
Probable	7 (7)	10	20 (17)	37	40 (31)	83	43 (32)	89	103 (26)	254	110 (22)	219
Possible	12 (11)	18	8 (7)	11	21 (16)	27	16 (12)	32	45 (11)	80	57 (12)	88
Unlikely	56 (52)	124	53 (45)	129	69 (53)	189	69 (51)	176	191 (50)	494	247 (51)	618
Severity												
Mild	50 (47)	93	50 (43)	104	69 (53)	201	72 (54)	189	191 (50)	494	241 (49)	587
Moderate	29 (27)	53	32 (27)	66	43 (33)	86	44 (33)	104	119 (31)	256	148 (30)	309
Severe	4 (4)	6	5 (4)	7	8 (6)	12	3 (2)	4	16 (4)	23	20 (4)	29
Seriousness												
Not serious	60 (56)	146	63 (54)	171	87 (66)	296	87 (65)	290	237 (62)	757	297 (61)	905
Serious	3 (3)	4	5 (4)	6	3 (2)	3	6 (4)	7	14 (4)	16	17 (3)	20
Most common ^b												
Oral pruritus	4 (4)	4	14 (12)	15	23 (18)	31	27 (20)	31	64 (17)	77	68 (14)	81
Throat irritation	1 (<1)	1	3 (3)	3	5 (4)	5	8 (6)	10	16 (4)	18	17 (3)	19
Ear pruritus	2 (2)	2	5 (4)	7	8 (6)	9	15 (4)	18	15 (3)	18		
Mouth edema	3 (3)	3	3 (2)	3	11 (8)	12	17 (4)	18	17 (3)	18		
Paresthesia oral	1 (<1)	1	2 (2)	2	4 (3)	5	7 (5)	10	13 (3)	7	14 (3)	18
Mucosal edema	6 (5)	6	3 (2)	3	9 (2)	9	9 (2)	9				
Pharyngolaryngeal pain	2 (2)	2	3 (3)	4	2 (2)	3	7 (5)	9	12 (83)	16	14 (3)	18
Bronchitis	3 (3)	6	4 (3)	7	6 (5)	8	1 (<1)	1	11 (3)	16	14 (3)	22
Pharyngitis	3 (3)	3	10 (9)	12	8 (6)	9	1 (<1)	1	19 (5)	22	22 (4)	25
Asthma	5 (5)	6	6 (5)	7	12 (9)	17	12 (9)	19	30 (8)	43	35 (7)	49
Upper respiratory tract infection	9 (8)	11	9 (8)	12	7 (5)	8	9 (7)	9	25 (7)	29	34 (7)	40

Abbreviation: AEs, adverse events.

^aData are presented as number of subjects (percentage in treatment group with the event) and number of events (E).^bReported by at least 5% of subjects in any of the active treatment groups.

to impaired quality of life.⁴ The present data suggest that quality of life was ameliorated by 1 year of treatment with 6 SQ-HDM compared with placebo.

Whether improved control of AR contributes to improved control of coexisting AA has been discussed.²⁶ Acknowledging that AR and AA representing opposite ends of the same inflammatory disease continuum, guidelines recommend that treatment strategies target AA and AR.²⁷ The present data combined with data presented in the publication of the primary results suggest that the SQ HDM SLIT-tablet has a beneficial effect on HDM AR and AA within the same population.

An interesting observation from the dataset is that a statistically significantly larger proportion of subjects with a TCRS = 0 during baseline used a daily ICS dose > 400 µg budesonide at baseline compared with subjects using an ICS dose ≤ 400 µg at baseline (23% and 16%, respectively). The data suggest that in this trial subjects with a daily ICS use > 400 µg budesonide were less likely to report problems from their diagnosed HDM AR than those who took a daily ICS dose ≤ 400 µg budesonide. This finding has led to an upper limit of ICS use in a subsequent phase III trial with the SQ HDM SLIT-tablet that is designed to confirm the efficacy of the SQ HDM SLIT-tablet in a population with more severe rhinitis (EudraCT, no 2011-002277-38).

As for the entire trial population, most AEs observed in the trial were mild local allergic reactions that resolved spontaneously after a few weeks or months. The most frequent AE in this trial was oral pruritus; this is a mild local reaction that is common and expected with SLIT-tablets, because the oral mucosa is directly exposed to the allergen. Several asthma-related AEs were reported, especially in the ICS adjustment periods. A certain increase in asthma symptoms during these periods was to be expected to determine the lowest level of ICS necessary to control asthma. There were no indications of any change in frequency after initiation of treatment. Neither severe systemic allergic reactions nor any other life-threatening reactions were reported. Thus, the safety profile of the SQ HDM SLIT-tablet in the doses applied in this trial was substantially more benign than that usually observed for subcutaneously administered immunotherapy. A more

detailed description of the overall safety data is found in the primary publication.³

The observed safety profile warrants investigation of a higher dose, which also might lead to a greater difference between active treatment and placebo. Previously, doses up to 32 SQ-HDM have been investigated in phase I, and a dose of 16 SQ-HDM was found to be the highest tolerable dose in the short term but with a tolerability profile that could impair compliance in a setting of daily use over a period of several years.⁹

The mean symptom and medication scores in the subgroup of subjects with a TCRS > 0 suggest that the disease level was mild. Nonetheless, a statistically significant effect was found in the highest dose group, and, hypothetically, subjects with more severe symptoms and considerable room for improvement might benefit to a greater degree from treatment with the SQ HDM SLIT-tablet. The mild nature of AR symptoms in the trial population can be explained by the circumstance that the primary objective of the trial was to evaluate the effect of the SQ HDM SLIT-tablet on asthma. The requirement for concomitant HDM AR was included to increase the likelihood that the asthma of the enrolled subjects was related to HDM. For this reason, a clinical history of HDM AR was sufficient as an inclusion criterion, but with no quantitative requirements to the presence of symptoms or medication use at the time of enrollment. The mild level of AR became evident during the assessment of symptoms and medication scores during the 4-week baseline period. A considerable proportion of subjects (110 [18%] of entire trial population) were included in the trial based on a positive history of AR, but in fact had no symptoms or medication use (TCRS = 0) during the entire 4-week baseline period and therefore no room for improvement. This could explain why the prespecified end points for the evaluation of the efficacy of the SQ HDM SLIT-tablet in rhinoconjunctivitis did not show a statistically significant difference between active treatment and placebo. Another limitation to the present efficacy results is the fact that it is a post hoc subgroup analysis. Future trials should include subjects with clear evidence of AR, more severe symptoms, and need for medication use at inclusion. Furthermore, an additional higher dose (12 SQ-HDM)

has been included in an ongoing phase III trial with the SQ HDM SLIT-tablet, because the focus remains on the aspect of optimized risk and benefit.

As reported previously,³ the analysis of the primary end point in this trial showed that the SQ HDM SLIT-tablet significantly reduced the use of ICS in AA compared with placebo. Taken together, the 2 publications contribute to the proof of concept for the treatment of underlying HDM respiratory allergic disease with the SQ HDM SLIT-tablet, regardless of the dominant manifestation.

Appendix

The authors present this publication on behalf of all the involved investigators: **Denmark:** Holger Mosbech, Vibeke Backer, Lars Frølund, Jens Korsgaard, Ronald Dahl, Peter Lange, Thomas Jon Jensen; **France:** Frédéric de Blay, François Durand-Perdriel, Jean-Charles Farousz, James Le Sellin, François Wessel, Bernard Pigearias, Dominique Basset, Sami Taieb, Jacques Gayraud, M. Tunon de Lara; **Germany:** Ekkehard Beck, Albrecht Buße, Margitta Worm, Christian Schoch, Regina Deckelmann, Hans-Josef Graf, Bettina Hauswald, Claus Baumgarten, Nicolas Hunzelmann, Peter-Uwe Haase, Brigitta Becker, Peter Eberle, Thomas Ginko, Werner Heppt, Ludger Klimek, Axel Overlack, Claus Keller, Andrea von Berg, Sylvia Schnitzer, Christian Vogelberg; **Italy:** Agostino Cirillo, Nunzio Crimi, Carlo Lombardi, Mario di Gioacchino, Floriano Bonifazi, Sebastiano Gangemi, Constantino Troise, Anna Elide Pastorello, Giorgio Walter Canonica; **Spain:** Antonio Pelaez, Tamin Malek, Pedro Guardia, Ana Maria Plaza, Ana Isabel Tabar, Luis Prieto; **Sweden:** Sonja Werner, Max Jessen, Inga Malcus; **United Kingdom:** Stephen R. Durham, Anne Fay, Philip Wood, Philip Doré, C. Corrigan, K. Rajakulasingham, Aarnoud Huissoon, H.S. Jenkins, Alaisdair Stewart, Runa Ali, Glenis K. Scadding; **Poland:** Andrzej Dyczek, K. Janh-Rózyk, E. Springer, E. Rogala, Ewa Bogacka, E. Trebas-Pietras, P. Kuna, Iwona Steiner, Karolina Kukawska, E. Jassem, Jozef Malolepszy, Krzysztof Buczylo, Krystyna Rybka, Teresa Stelmasiak, R. Gawlik.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.11.015>.

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eMethods

Prespecified Extrapulmonary Assessments, End Points, Statistics, and Conclusion

Daily rhinoconjunctivitis symptom and medication scores

Six rhinoconjunctivitis symptoms (4 nose symptoms and 2 eye symptoms) were assessed on a scale from 0 to 3 (no symptoms to severe symptoms).

The total daily rhinoconjunctivitis symptom score was calculated for each patient as the sum of all individual symptom scores. Thus, the maximum total daily rhinoconjunctivitis symptom score was 18.

The total daily rhinoconjunctivitis medication score is the sum of the total daily scores for each medication. The individual total daily medication score was calculated as the unit score multiplied by the number of units entered in the daily diary by the patient. The maximum daily rhinoconjunctivitis medication score was 30.

For each patient, the average total daily rhinoconjunctivitis symptom score and the average total daily rhinoconjunctivitis medication score (average rhinoconjunctivitis symptom and medication scores) were calculated

- during the pretreatment ICS tapering period (from visit 2 to 4 weeks before visit 3)
- during the pretreatment ICS stable period (baseline period, the last 4 weeks before visit 4)
- during the end-of-treatment ICS tapering period (from visit 10 to 4 weeks before visit 12, ie, end-of-trial visit)
- during the end-of-treatment ICS stable period (the last 4 weeks before visit 12, ie, end-of-trial visit)

Statistics. The total daily rhinoconjunctivitis symptom and medication scores were averaged over the end-of-treatment ICS stable period (the last 4 weeks before visit 12, ie, end-of-trial visit) for each patient and analyzed similarly to the primary end point by a

linear mixed model using data from all treatment groups. The model included treatment group and average score during the pretreatment ICS stable period (baseline) as fixed effects and center as a random effect. Two-sided 95% confidence intervals for the adjusted mean differences and corresponding *P* values are presented. These were defined in the statistical analysis plan.

The RQLQ(S)

The RQLQ(S) consists of 28 items (questions) in 7 domains, with each scored on a 7-point scale (0, no impairment; 6, maximum impairment). Patients were to respond to each question after recalling their experience during the past week. The 7 domains are activities, sleep, non-nose and non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.

Statistics. Overall scores and domain scores were calculated for each patient at randomization and initiation of treatment (visit 4, baseline) and at visit 12 (end-of-trial visit). The change from baseline to the end of the trial also was calculated for each patient.

Overall and domain scores at visit 12 (end-of-trial visit) were analyzed similarly to the primary end point with a linear mixed model including treatment group and baseline value as fixed effects and center as a random effect.

Conclusion of prespecified extrapulmonary end points

A statistically significant difference between the 6-development units group and placebo was observed for the overall RQLQ(S) score (*P* = .0164). This difference was driven primarily by the sleep domain and the non-nose and non-eye symptoms domain (fatigue, thirst, decreased productivity, tiredness, poor concentration, headache, and weariness).

No difference between active treatment and placebo was detected by rhinoconjunctivitis symptom and medication scores or for the conjunctival provocation test or skin prick test results.

eTable 1

ICS use and its relation to the total combined rhinitis score

ICS	TCRS = 0 n (%)	TCRS > 0 n (%)
ICS ≤ 400 µg	57 (16%)	308 (4%)
ICS > 400 µg but ≤ 800 µg	53 (23%)	181 (77%)

Abbreviations: TCRS, total combined rhinitis score; ICS, inhaled corticosteroid (budesonide).

The proportion of subjects scoring TCRS = 0 at baseline was higher for subjects with a daily ICS dose above 400 µg budesonide at baseline than for subjects with ICS at or below 400 µg budesonide at baseline, namely 23% vs. 16%. In other words, subjects were more likely to score zero (ie., experience no problems from their house dust mite allergic rhinitis) if their daily ICS dose was above 400 µg than if it was below 400 µg. This difference was statistically significant (*P* = .0301).