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ORIGINAL RESEARCH

A Real-Life One-Year Non-Interventional Study Assessing Safety, Tolerability, and Treatment Outcome of the SQ HDM SLIT-Tablet (Acarizax®) in House Dust Mite Allergic Rhinitis With or Without Asthma

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ABSTRACT

Introduction: The aim of this study was to investigate the safety profile, tolerability, and outcome of the SQ® house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet after 1 year of treatment in clinical practice among adults with HDM-related allergic rhinitis (AR) ± allergic asthma (AA).

Methods: In a non-interventional multicenter, observational study, patients were followed at 3 visits for 1 year. Adverse events (AE) were recorded at all visits. Patients graded their allergic symptoms as none, mild, moderate, or severe, and recorded AR and AA medication use. Asthma symptom control was assessed according to the Global Initiative for Asthma (GINA).

Results: One hundred and ninety-eight patients were included; 115 (58%) had AR without asthma and 83 (42%) had both AR and AA. One hundred and sixty-six (84%) patients completed the study. Eighty percent of patients experienced an AE: 151 (75%) AEs were mild, 42 (21%) moderate, and 4 (2%) severe. Three patients (1.5%) reported four events that were considered serious (SAEs). One SAE was considered possibly treatment-related. No anaphylactic reactions occurred. The proportion of patients experiencing allergy symptom reductions by at least one step were 75% (nasal), 62% (eye), 16% (skin), and 13% (other symptoms); 75% of patients with AA experienced a decrease of at least one step in bronchial symptoms. AR medication and inhaled corticosteroids were statistically significant reduced.

Conclusion: The SQ HDM SLIT-tablet was safe and well tolerated; the type, frequency, and severity of AEs resembled what RCTs have previously demonstrated. As explorative endpoints, statistically significant reductions in AR and AA symptoms and medication use were seen along with improved asthma control after 1 year of treatment, implying that clinically meaningful changes were seen after 1 year of treatment with the SQ HDM SLIT-tablet.

Keywords: Allergic asthma; Allergic rhinitis; Allergy immunotherapy; House dust mite allergy; SQ SLIT-tablet; Tolerability

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41030-021-00150-z.

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Key Summary Points

Why carry out this study?

House dust mite (HDM) allergy is strongly implicated in the pathogenesis of allergic rhinitis (AR) and allergic asthma (AA).

Allergen avoidance is difficult to achieve, and symptomatic medication may be inadequate in providing symptom relief.

Allergy immunotherapy (AIT) addresses the underlying etiology of allergic disease by modifying the immunological response to the causative allergen, and provides clinically meaningful symptom relief, reduces the need for medication, and improves the quality of life of patients.

This study evaluated the safety and tolerability of the SQ HDM SLIT-tablet after 1 year of treatment in a real-life clinical setting in adults with HDM AR with or without AA in Sweden and Denmark, and exploratively assessed the treatment outcome.

What was learned from the study?

The SQ HDM SLIT-tablet was safe and well tolerated.

As explorative endpoints, statistically significant reductions in AR and AA symptoms and medication use were seen along with improved asthma control after 1 year of treatment, implying that clinically meaningful changes were seen after 1 year of treatment with the SQ HDM SLIT-tablet.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13713868.

INTRODUCTION

House dust mite (HDM) allergy is strongly implicated in the pathogenesis of allergic rhinitis (AR) and allergic asthma (AA). In Europe, the prevalence of AR is 17–29% [1], which is similar in the Nordic countries [2, 3]. The prevalence of asthma in the Nordic countries is around 7–10%, of which half of the adults are estimated to have AA [4]. Almost all patients who have HDM-induced AA also have AR, while around half of patients with HDM AR also have asthma [5]. Approximately 50% of patients with AA, AR or both are sensitized to HDM, primarily to the species *Dermatophagoides* (*D.*) *pteronyssinus* and *D. farinae* [1, 6, 7].

HDM allergen avoidance is difficult to achieve to an extent that will provide clinically relevant symptom relief for respiratory allergy [8–11]. Symptomatic medication [e.g. oral or topical antihistamines, nasal corticosteroids (NCS), inhaled corticosteroids (ICS), and bronchodilators] may reduce symptoms; however, inadequate symptom control and dissatisfaction with treatment can be high [12, 13].

Allergy immunotherapy (AIT) is the only treatment option for AR and AA that addresses the underlying etiology of allergic disease by modifying the immunological response to the causative allergen. AIT has been shown to provide clinically meaningful symptom relief, reduce the need for medication, and improve the quality of life of patients [9, 14]. Further, sublingual immunotherapy (SLIT) in a tablet formulation is associated with less severe adverse events than subcutaneous immunotherapy (SCIT) and offers improved patient convenience [15], although SCIT in experienced hands is also considered a safe treatment [16].

The safety and efficacy profile of the SQ HDM SLIT-tablet (ACARIZAX®, ALK-Abelló A/S, Hørsholm, Denmark) for treatment of HDM AR or AA has been evaluated and described in several randomized controlled trials (RCT) [17–19]. The purpose of this study was to evaluate the

safety and tolerability and as an explorative endpoint to evaluate the treatment outcome of the SQ HDM SLIT-tablet after 1 year of treatment in a real-life clinical setting in adults with HDM AR with or without AA in Sweden and Denmark.

METHODS

Adults (18–65 years) with HDM allergy were followed in a non-interventional multicenter, observational study and consecutively enrolled from September 2016 through December 2017 in routine clinical practice. Patients eligible for treatment with the SQ HDM SLIT-tablet had a clinical history of HDM allergy and a positive test for HDM sensitization (positive skin prick test and/or positive specific IgE) along with (a) persistent moderate to severe HDM AR despite use of symptom-relieving medication or (b) HDM AA not well controlled by ICS and associated with mild to severe HDM AR. Treatment with the SQ HDM SLIT-tablet was prescribed and used according to the label, and at that time the age group according to the summary of product characteristics/label was 18–65 years. A few patients with relevant HDM allergy but outside this age group were treated; they should not have been enrolled in the study and were therefore excluded from follow-up analyses. Patients' asthma status should be carefully evaluated before the initiation of treatment. Exclusion criteria were in alignment with the contraindications to the SQ HDM SLIT-tablet and comprised hypersensitivity to any of the excipients of the tablet, forced expiratory volume in the first second (FEV1) < 70% of predicted value after adequate pharmacological treatment at initiation of treatment, severe asthma exacerbation within the last 3 months, acute respiratory tract infection in patients with asthma, active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression, malignant neoplastic diseases with current disease relevance, acute severe oral inflammation, or oral wounds. Patients provided written informed consent prior to enrollment.

The study comprised three visits: the first administration of SQ HDM SLIT-tablet, collection of baseline characteristics, and prescription of 30 HDM SLIT-tablets (visit 1); the first follow-up after 1 month (visit 2); and the second follow-up 12 months after first administration (visit 3). Visit 2 was either a telephone interview or a visit at the clinic or hospital. The final visit after an observation period of approximately 12 months corresponded to the duration of the clinical trials [17, 19] and was chosen to achieve comparability of results given the seasonality of HDM allergy symptoms [20]. For patients discontinuing treatment before 12 months, the final visit was conducted at the time of discontinuation.

Adverse events (AE) were recorded at all planned and unscheduled visits. Patients graded symptoms as none, mild, moderate, or severe, and recorded medication use. Asthma symptom control was assessed according to the Global Initiative for Asthma (GINA) [8].

Explorative objectives of the study were to assess the symptoms and medication use over the course of the study comparing end-of-study levels with baseline levels. At baseline, allergy symptoms during the last 12 months were recorded, including nose symptoms, eye symptoms, bronchial symptoms, skin symptoms, and other. Additionally, the grade of allergy symptoms was defined as follows; none: no symptoms at all; mild: transient symptoms, no interference with the patient's daily activities; moderate: marked symptoms, moderate interference with the patient's daily activities; severe: considerable interference with the patient's daily activities, unacceptable. As an explorative outcome, the patients' symptoms in each category were assessed at follow-up visits to record changes from baseline over the course of the study. AR symptoms were graded by the physician by questioning the patient. Asthma symptom control in the AA group was assessed according to GINA 2015 [8] and lung function tests at baseline and follow-up visits.

Statistics: Descriptive statistics were applied. For comparison of changes over time, the sign test was used for categorical variables.

The study was conducted in Denmark and Sweden. All patients provided informed consent

to participate in the study. For this non-interventional study, ethics committee approval was required in Sweden only, and this was obtained from Regionala Etikprövningsnämnden prior to the study initiation (no. 3964-001). The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments Regarding the Danish National Ethics Committee guidelines, please visit: https://www.nvk.dk/~/media/NVK/Dokumenter/Vejledning_Engelsk.pdf, Sect. 2.2.2

RESULTS

Two hundred and two patients (safety population) received the SQ HDM SLIT-tablet at the first visit and comprised the safety population, i.e., the full analysis set (FAS). Four patients (13, 66, 71, and 76 years) were wrongly included due to age and were therefore excluded from the population (intention to treat, ITT, $n = 198$) that was used to describe changes in symptoms and medication use. The mean age was 38 years. One hundred and fifteen patients (58%) had AR without asthma (AR only) and 83 (42%) had both AR and AA (AR + AA) (Table 1).

The vast majority (193 [98%]) of the patient population were Caucasian and 5 patients (2%) were Asian by ethnicity. Patients were enrolled from Swedish and Danish hospital-based allergy clinics and private practicing specialists; in total 25 centers participated.

Based on the safety population, 161 patients (80%) experienced an AE (E = 427) from visit 1 through visit 3. Of these, 151 patients (75%) reported AEs to be mild, 42 patients (21%) reported AEs to be moderate, and 4 patients (2%) reported AEs to be severe. AEs reported by > 5% of patients by preferred term are tabulated in Table 2.

Three patients (1.5%) had four events that were considered serious; one SAE was considered possibly treatment-related; one patient experienced dyspnea after 2 months of treatment. The patient was hospitalized, treated with prednisolone, recovered, and discontinued treatment. It was reported that dyspnea was also possibly related to the patient's pre-existing medical history of grass pollen allergy. Three other SAEs (in two patients) were considered not treatment-related: One patient experienced (1) viral bronchitis and (2) a lung infection after approximately 2 months of treatment. The patient continued treatment. Another patient suffered from (3) depression and discontinued treatment. None of these two patients had an established asthma diagnosis at inclusion.

No anaphylactic reactions occurred during the study, and no adrenaline was administered.

One hundred and sixty-six (84%) of 198 patients completed the study and had data recorded at visit 3. Among 32 patients discontinuing treatment prematurely, the reasons were: AE ($n = 15$), lost to follow-up ($n = 13$), withdrawal of consent ($n = 2$), other reasons ($n = 1$), and lack of efficacy ($n = 1$). The characteristics of the patients who discontinued treatment were as follows: The female/male ratio was 26 (81%)/6. The mean age was 37 years (median 36.5 years, range 20–60). Twenty-four patients (75%) had moderate disease, while 8 patients (25%) had mild disease; 24 patients (75%) had multiple allergies and 8 patients (25%) had only HDM allergy.

Two pregnancies were reported during the study: In one case of pregnancy, the treatment was continued; the pregnancy outcome was one healthy child born by normal delivery, and no pregnancy-related complications were reported. In the other case of pregnancy, treatment was discontinued; the pregnancy outcome was spontaneous abortion in week 11.

Allergic symptoms from the nose and the eyes generally improved over time from visit 1 to visit 3 in the ITT population as well as in the subgroups (Table 3).

Asthma symptom control according to GINA 2015[8] was assessed at all visits. 21 (32%) patients obtained an improvement of asthma control of at least one step from visit 1 to visit 3, $p = 0.013$. Further, a significant proportion of patients with AR + AA experienced a reduction in daytime asthma symptoms along with reduction in night awakening due to asthma (Table 4).

The number of patients experiencing reductions in AR symptom medications of at least one step (conjunctival, nasal, oral antihistamines, as well as NCS) from visit 1 to visit 3 was

Table 1 Baseline characteristics of the intention-to-treat population (n = 198), in the total population and by subgroup [allergic rhinitis without asthma (AR only) and allergic rhinitis with asthma (AR + AA)]

Variable	Total (n = 198)	AR only (n = 115)	AR + AA (n = 83)
Age (years)			
Mean (SD) [95 CI]	38 (11.7) [35.8; 39.1]	38 (11.2) [36.1; 40.2]	37 (12.5) [33.8; 39.2]
Median (range)	37 (18; 61)	37 (18; 60)	36 (18; 61)
Gender; male/female (%)	89/109 (55)	56/59 (51)	33/50 (60)
Height (cm)			
Mean (SD) [95 CI]	173 (10.3) [171.6; 174.5]	174 (10.0) [172.2; 175.9]	172 (10.7) [169.3; 174.0]
Median (range)	173 (150; 196)	175 (151; 196)	169 (150; 193)
Weight (kg)			
Mean (SD) [95 CI]	76 (16.6) [73.9; 78.5]	78 (17.4) [74.4; 80.9]	74 (15.3) [70.8; 77.5]
Median (range)	73 (50; 133)	75 (50; 133)	70 (50; 132)
Country			
Denmark	98 (49)	59 (51)	39 (47)
Sweden	100 (51)	56 (49)	44 (53)
History of allergy			
Allergy in need of treatment with allergy immunotherapy			
House dust mites	198 (100)	115 (100)	83 (100)
Tree (birch, alder, hazel)	26 (13)	15 (13)	11 (13)
Grass	53 (27)	31 (27)	22 (27)
Animal hair/dander	19 (10)	12 (10)	7 (8)
Weed	0 (0)	0 (0)	0 (0)
Other	7 (4)	3 (3)	4 (5)
Age at first allergic rhinitis	n = 191	n = 112	n = 79
Mean (SD) [95 CI]	18 (11.5) [16.6; 19.9]	20 (11.2) [17.8; 22.0]	16 (11.7) [13.3; 18.5]
Median (range)	15 (0; 57)	17.5 (2; 51)	13 (0; 57)
Age at first allergic asthma	n = 90	n = 12	n = 78
Mean (SD) [95 CI]	19 (14.7) [15.7; 21.9}	19 (14.4) [9.7; 28.0]	19 (14.9) [15.5; 22.2]
Median (range)	14 (0; 59)	11.5 (4; 50)	14 (0; 59)
Age at house dust mite allergy diagnosis	n = 193	n = 112	n = 81
Mean (SD) [95 CI]	25 (14.3) [22.8; 26.8]	28 (14.4) [25.4; 30.8]	20 (12.8) [17.4; 23.0]
Median (range)	22 (0; 60)	28 (4; 60)	17 (0; 58)

Table 1 continued

Variable	Total (n = 198)	AR only (n = 115)	AR + AA (n = 83)
Years since dust mite allergy diagnosis	n = 193	n = 112	n = 81
Mean (SD) [95 CI]	13 (12.8) [10.9; 14.6]	10 (11.7) [7.8; 12.2]	17 (13.2) [13.7; 19.5]
Median (range)	9 (0; 49)	6 (0; 49)	14 (0; 45)
Other clinical manifestations of the house dust mite allergy			
Conjunctivitis	142 (72)	82 (71)	60 (72)
Atopic dermatitis	34 (17)	16 (14)	18 (22)
Other	32 (16)	24 (21)	8 (10)
Concomitant allergies			
Tree (birch, alder, hazel)	73 (37)	46 (40)	27 (33)
Grass	103 (52)	60 (52)	43 (52)
Animal hair/dander	91 (46)	51 (44)	40 (48)
Weed	9 (5)	4 (4)	5 (6)
Mold	7 (4)	3 (3)	4 (5)
Food	10 (5)	6 (5)	4 (5)
Other	8 (4)	4 (4)	4 (5)

For categorical variables, n (%) is presented
For continuous variables, mean (SD) [95 CI for mean] / median (min; max) / n = is presented if different from the total ITT population = 198; subgroup without asthma n = 115, and subgroup with asthma n = 83. *AR* allergic rhinitis; *AA* allergic asthma

Table 2 Adverse events reported by > 5% of patients listed by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, based on the safety population (FAS) (n = 202)

Preferred term	Safety population (n = 202)	
	Events	Subjects with events n (%)
Oral pruritus	116	107 (53)
Throat irritation	47	43 (21)
Ear pruritus	44	40 (20)
Mouth swelling	19	18 (9)
Eye pruritus	17	16 (9)

consistently significant in the ITT population as well as in the AR only subgroup and AR + AA subgroup (Table 5). Asthma medication was lowered in the AA + AR subgroup over time; specifically, ICS and short-acting beta-2 agonists were reduced from visit 1 to visit 3 by 20% (p = 0.013) and 23% (p = 0.0044), respectively (Table 5). Extensive overviews of all allergy and asthma medication use over visits by type of medication and by patient group are available in the online repository.

DISCUSSION

Main Findings

The SQ HDM SLIT-tablet was safe and well tolerated in this observational study. The type, frequency, and severity of AEs were like what RCTs have previously demonstrated [17–19]. Statistically significant and clinically relevant

Table 3 The proportion of patients experiencing symptom reductions by at least one step from visit 1 to 3 in the total ITT population (n = 198) in the upper part, patients with AR only (n = 115) in the middle part, and patients with AR + AA (n = 83) in the lower part of the table

Symptoms reported in the ITT population	Visit 1 n = 198 (%)	Visit 2 n = 191 (%)	Visit 3 n = 166 (%)	Change from Visit 1 to Visit 2	Change from Visit 1 to Visit 3
Nose					
No symptoms	3 (2)	26 (14)	45 (27)	Decrease 98 (52)	Decrease 124 (75)
Mild symptoms	30 (15)	73 (38)	75 (45)	Equal 85(44)	Equal 40 (24)
Moderate symptoms	86 (43)	59 (31)	37 (22)	Increase 7(4)	Increase 2/(1)
Severe symptoms	79 (40)	32 (17)	9 (6)	$p \leq 0.0001$	$p \leq 0.0001$
Eyes					
No symptoms	40 (20)	77 (40)	98 (59)	Decrease 83(44)	Decrease 103 (62)
Mild symptoms	57 (29)	65 (34)	51 (31)	Equal 95 (50)	Equal 61 (37)
Moderate symptoms	71 (36)	37 (20)	17 (10)	Increase 12(6)	Increase 2(1)
Severe symptoms	30 (15)	11 (6)	0 (0)	$p = < 0.0001$	$p < 0.0001$
Bronchial					
No symptoms	83 (42)	101 (53)	107 (64)	Decrease 51 (27)	Decrease 77 (46)
Mild symptoms	51 (26)	45 (24)	52 (31)	Equal 122 (64)	Equal 82 (50)
Moderate symptoms	49 (25)	34 (18)	6 (4)	Increase 17 (9)	Increase 7(4)
Severe symptoms	15 (7)	10 (5)	1 (1)	$p \leq 0.0001$	$p \leq 0.0001$
Skin					
No symptoms	140 (71)	148 (78)	139 (84)	Decrease 26 (14)	Decrease 26 (16)
Mild symptoms	31 (16)	28 (15)	19 (12)	Equal 159 (84)	Equal 134 (81)
Moderate symptoms	19 (9)	12 (6)	5 (3)	Increase 9 (5)	Increase 5 (3)
Severe symptoms	8 (4)	2 (1)	2 (1)	$p = 0.0002$	$p = 0.0002$
Other					
No symptoms	172 (87)	168 (88)	156 (94)	Decrease 12 (6)	Decrease 21 (13)
Mild symptoms	8 (4)	10 (5)	8 (5)	Equal 169 (89)	Equal 140 (84)
Moderate symptoms	13 (7)	9 (5)	2 (1)	Increase 9 (5)	Increase 5 (3)
Severe symptoms	5 (2)	3 (2)	0 (0)	$p = 0.66$	$p = 0.0025$
Symptoms reported in patients with AR only	**Visit 1 n = 115 (%)**	**Visit 2 n = 110 (%)**	**Visit 3 n = 95 (%)**	**Change from Visit 1 to Visit 2**	**Change from Visit 1 to Visit 3**
Nose					
No symptoms	1 (1)	10 (9)	25 (26)	Decrease 62 (56)	Decrease 68 (72)
Mild symptoms	12 (10)	47 (43)	41 (43)	Equal 41 (37)	Equal 26 (27)

Table 3 continued

Symptoms reported in patients with AR only	Visit 1 *n* = 115 (%)	Visit 2 *n* = 110 (%)	Visit 3 *n* = 95 (%)	Change from Visit 1 to Visit 2	Change from Visit 1 to Visit 3
Moderate symptoms	52 (45)	32 (29)	22 (23)	Increase 7 (7)	Increase 1 (1)
Severe symptoms	50 (44)	21 (19)	7 (8)	$p \leq 0.0001$	$p \leq 0.0001$
Eyes					
No symptoms	23 (20)	44 (40)	57 (60)	Decrease 52 (47)	Decrease 56 (59)
Mild symptoms	32 (28)	43 (39)	27 (28)	Equal 51 (46)	Equal 38 (40)
Moderate symptoms	46 (40)	17 (16)	11 (12)	Increase 7(7)	Increase 1 (1)
Severe symptoms	14 (12)	6 (5)	0 (0)	$p \leq 0.0001$	$p \leq 0.0001$
Bronchial					
No symptoms	81 (70)	81 (74)	82 (86)	Decrease 18 (16)	Decrease 24 (25)
Mild symptoms	24 (21)	23 (21)	13 (14)	Equal 80 (73)	Equal 65 (69)
Moderate symptoms	8 (7)	4 (3)	0 (0)	Increase 12 (11)	Increase 6 (6)
Severe symptoms	2 (2)	2 (2)	0 (0)	$p = 0.36$	$p = 0.0014$
Skin					
No symptoms	86 (75)	90 (82)	83 (88)	Decrease 12 (11)	Decrease 12 (13)
Mild symptoms	17 (15)	12 (11)	7 (7)	Equal 97 (88)	Equal 79 (83)
Moderate symptoms	7 (6)	6 (5)	3 (3)	Increase 1 (11)	Increase 4 (4)
Severe symptoms	5 (4)	2 (2)	2 (2)	$p = 0.0034$	$p = 0.077$
Other					
No symptoms	99 (86)	100 (90)	93 (98)	Decrease 9 (8)	Decrease 12 (13)
Mild symptoms	5 (4)	5 (5)	2 (2)	Equal 97 (88)	Equal 81 (85)
Moderate symptoms	8 (7)	4 (4)	0 (0)	Increase 4 (4)	Increase 2 (2)
Severe symptoms	3 (3)	1 (1)	0 (0)	$p = 0.27$	$p = 0.013$
Symptoms reported by patients with AR + AA	**Visit 1 *n* = 83 (%)**	**Visit 2 *n* = 81 (%)**	**Visit 3 *n* = 71 (%)**	**Change from Visit 1 to Visit 2**	**Change from Visit 1 to Visit 3**
Nose					
No symptoms	2 (2)	16 (20)	20 (28)	Decrease 36 (45)	Decrease 56 (79)
Mild symptoms	18 (22)	26 (32)	34 (48)	Equal 44 (55)	Equal 14 (20)
Moderate symptoms	34 (41)	27 (34)	15 (21)	Increase 0 (0)	Increase 1 (1)
Severe symptoms	29 (35)	11 (14)	2 (3)	$p \leq 0.0001$	$p \leq 0.0001$

Table 3 continued

Symptoms reported by patients with AR + AA	Visit 1 n = 83 (%)	Visit 2 n = 81 (%)	Visit 3 n = 71 (%)	Change from Visit 1 to Visit 2	Change from Visit 1 to Visit 3
Eyes					
No symptoms	17 (21)	33 (41)	41 (58)	Decrease 31 (39)	Decrease 47 (66)
Mild symptoms	25 (30)	22 (28)	24 (34)	Equal 44 (55)	Equal 23 (33)
Moderate symptoms	25 (30)	20 (25)	6 (8)	Increase 5 (6)	Increase 1 (1)
Severe symptoms	16 (19)	5 (6)	0 (0)	$p \leq 0.0001$	$p \leq 0.0001$
Bronchial					
No symptoms	2 (2)	20 (25)	25 (35)	Decrease 33 (41)	Decrease 53 (75)
Mild symptoms	27 (33)	22 (27)	39 (55)	Equal 42 (53)	Equal 17 (24)
Moderate symptoms	41 (49)	30 (38)	6 (9)	Increase 5 (6)	Increase 1 (1)
Severe symptoms	13 (16)	8 (10)	1 (1)	$p \leq 0.0001$	$p \leq 0.0001$
Skin					
No symptoms	54 (65)	58 (72)	56 (80)	Decrease 14 (17)	Decrease 14 (20)
Mild symptoms	14 (17)	16 (20)	12 (17)	Equal 62 (78)	Equal 55 (79)
Moderate symptoms	12 (14)	6 (8)	2 (3)	Increase 4 (5)	Increase 1 (1)
Severe symptoms	3 (4)	0 (0)	0 (0)	$p = 0.031$	$p = 0.0010$
Other	73 (88)	68 (85)	63 (89)		
No symptoms	3 (4)	5 (6)	6 (8)	Decrease 3 (4)	Decrease 9 (13)
Mild symptoms	5 (6)	5 (6)	2 (3)	Equal 72 (90)	Equal 59 (83)
Moderate symptoms	2 (2)	2 (3)	0 (0)	Increase 5 (6)	Increase 3 (4)
Severe symptoms				$p = 0.73$	$p = 0.15$

AA allergic asthma, *AR* allergic rhinitis, *n* number of patients, *ITT* intention-to-treat
For categorical variables, *n* (%) are presented
For comparison over time, the sign test was used for categorical variables

reductions in symptoms and medication use were seen in addition to improved asthma control after 1 year of treatment with the SQ HDM SLIT-tablet. In this routine clinical setting, a large proportion of patients completed the study.

Interpretation

Around 80% of patients experienced treatment-related AEs, of which around 75% were mild. The most commonly reported AEs (by ≥ 5% of patients) were oral pruritus, throat irritation, ear pruritus, mouth swelling, and eye pruritus. Both the type and mild character of the treatment-related AEs seen in this study resemble the safety and tolerability profile of the SQ HDM SLIT-tablet demonstrated in RCTs [17, 19]. Further, the event rate of SAEs was low; no anaphylactic reactions or fatalities occurred. No adrenaline was given. These findings are in accordance with the label of the SQ HDM SLIT-

Table 4 Number of patients experiencing asthma symptom control over time from visit 1 through visit 3 in the AR + AA subgroup (n = 83)

Variable	Visit 1 (n = 83) N (%)	Visit 2 (n = 81) N (%)	Visit 3 (n = 71) N (%)	Change from visit 1 to visit 2 N (%)	Change from visit 1 to visit 3 N (%)
Daytime asthma symptoms > twice/week	32 (40)	24 (31)	17 (25)	Decrease 10 (13)	Decrease 14 (21)
				Equal 62 (82)	Equal 50 (76)
				Increase 4 (5)	Increase 2 (3)
				p = 0.18	p = 0.0042
Night waking due to asthma	17 (21)	10 (13)	6 (9)	Decrease 6 (8)	Decrease 13 (20)
				Equal 69 (91)	Equal 51 (77)
				Increase 1 (1)	Increase 2 (3)
				p = 0.13	p = 0.0074
Reliever needed > twice/week	17 (21)	15 (20)	11 (16)	Decrease 7 (9)	Decrease 9 (14)
				Equal 63 (83)	Equal 53 (80)
				Increase 6 (8)	Increase 4 (6)
				p = 1.00	p = 0.27
Activity limitation due to asthma	22 (27)	16 (21)	13 (19)	Decrease 7 (9)	Decrease 10 (15)
				Equal 67 (88)	Equal 52 (79)
				Increase 2 (3)	Increase 4 (6)
				p = 0.18	p = 0.18
Level of asthma symptom control					
Well controlled	43 (52)	47 (61)	42 (63)	Decrease 17 (22)	Decrease 21 (32)
Partly controlled	21 (26)	19 (25)	17 (25)	Equal 52 (69)	Equal 38 (58)
Uncontrolled	18 (22)	11 (14)	8 (12)	Increase 7 (9)	Increase 7 (10)
				p = 0.064	p = 0.013

For categorical variables, n (%) is presented
For comparison over time, the sign test was used for categorical variables
Data are missing for level of asthma symptom control (visit 1 n = 82; visit 2 n = 77; visit 3 n = 67)

tablet and reflect a safety profile supporting at-home administration.

Oral pruritus was the most frequently reported type of AE, with the vast majority being mild. The exact duration of AEs was not captured in this study. However, a pooled analysis of data from RCTs investigating the SQ HDM SLIT-tablet in adults suggested that oral pruritus on average lasted 5 min post-administration and resolved after 6 days of treatment, throat irritation after 9 days, and mouth edema after 21 days (all for subjects on active treatment) [21]. The most frequent reason given for discontinuation in this study was AE, and experiencing an AE is by far the most frequently reported reason for treatment discontinuation in both RCTs and real-world studies with SLIT [17, 18, 21–23]. This points to

Table 5 Change over time from visit 1 to visit 3 in the number of patients using AR symptom medication and asthma medication in the ITT (intention-to-treat) population, AR only subgroup, and AR + AA subgroup

Variable	ITT (n = 198) Change from visit 1 to visit 3 N (%)	AR only (n = 115) Change from visit 1 to visit 3 N (%)	AR + AA (n = 83) Change from visit 1 to visit 3 N (%)
Antihistamines conjunctival	Decrease 37 (22)	Decrease 23 (24)	Decrease 14 (20)
	Equal 127 (77)	Equal 71 (75)	Equal 56 (79)
	Increase 2 (1)	Increase 1 (1)	Increase 1 (1)
	$p \leq 0.0001$	$p \leq 0.0001$	$p = 0.0010$
Antihistamines nasal	Decrease 38 (23)	Decrease 24 (25)	Decrease 14 (20)
	Equal 117 (71)	Equal 64 (68)	Equal 53 (75)
	Increase 11 (6)	Increase 7 (7)	Increase 4 (5)
	$p = 0.0001$	$p = 0.0033$	$p = 0.031$
Antihistamines oral	Decrease 55 (33)	Decrease 38 (40)	Decrease 17 (24)
	Equal 99 (60)	Equal 50 (53)	Equal 49 (69)
	Increase 12 (7)	Increase 7 (7)	Increase 5 (7)
	$p \leq 0.0001$	$p \leq 0.0001$	$p = 0.017$
NCS	Decrease 60 (36)	Decrease 37 (39)	Decrease 23 (32)
	Equal 103 (62)	Equal 57 (60)	Equal 46 (65)
	Increase 3 (2)	Increase 1 (1)	Increase 2 (3)
	$p \leq 0.0001$	$p \leq 0.0001$	$p \leq 0.0001$
ICS	Decrease 17 (10)	Decrease 3 (3)	Decrease 14 (20)
	Equal 145 (87)	Equal 91 (96)	Equal 54 (76)
	Increase 4 (3)	Increase 1 (1)	Increase 3 (4)
	$p = 0.0072$	$p = 0.63$	$p = 0.013$
LABA	Decrease 11 (7)	Decrease 1 (1)	Decrease 10 (14)
	Equal 151 (91)	Equal 93 (98)	Equal 58 (82)
	Increase 4 (2)	Increase 1 (1)	Increase 3 (4)
	$p = 0.12$	$p = 1.00$	$p = 0.092$

Table 5 continued

Variable	ITT (n = 198) Change from visit 1 to visit 3 N (%)	AR only (n = 115) Change from visit 1 to visit 3 N (%)	AR + AA (n = 83) Change from visit 1 to visit 3 N (%)
SABA	Decrease 21 (13)	Decrease 5 (5)	Decrease 16 (23)
	Equal 141 (85)	Equal 89 (94)	Equal 52 (73)
	Increase 4 (2)	Increase 1 (1)	Increase 3 (4)
	p = 0.0009	p = 0.22	p = 0.0044
Leukotriene receptor antagonist	Decrease 14 (8)	Decrease 5 (5)	Decrease 9 (13)
	Equal 146 (88)	Equal 88 (93)	Equal 58 (82)
	Increase 6 (4)	Increase 2 (2)	Increase 4 (5)
	p = 0.12	p = 0.45	p = 0.27

NCS nasal corticosteroids, *ICS* inhaled corticosteroids, *SABA* short-acting beta-2 agonists, *LABA* long-acting beta-2 agonists
For categorical variables, n (%) is presented
For comparison over time, the sign test was used for categorical variables

the need for careful patient education and information, in particular on AEs, along with close patient follow-up [22, 23].

The characteristics of discontinued patients in this study outline a median age of 36.5 years, a higher proportion of females than males, and that most patients who discontinued had moderate rather than mild disease. A real-world study with the SQ grass SLIT-tablet showed that among adults, younger age and a higher prevalence of reported oral and/or gastrointestinal side effects characterized the group that terminated treatment prematurely [22], whereas another real-world study showed somewhat higher treatment persistence in children compared to adults [23]. Additionally, the majority of discontinued patients in this study had multiple allergies. This may point to the clinical dilemma that AIT (SCIT or SLIT) might be indicated in several allergies simultaneously, which may be difficult to manage and challenging for the patient; this aspect, among several others (e.g., patient preferences), should be included in considering the choice of SLIT versus SCIT in such cases.

A feature of the tablet-based AIT is the daily dosing and self-administration, in which context the lack of treatment persistence has been pointed to as a major challenge [24–27]. A treatment duration of 3 years adds to this issue [23, 28–30]. In this study, a high proportion of patients completed the study. Notwithstanding the lack of tablet count or other measures of assessing treatment adherence herein, the completion rate in this study is high.

Although this study lasted only a year, this rate is comparable to real-world data on the SQ grass SLIT-tablet [22, 23] but higher than what has generally been reported on completion rates [24, 31] and prescription renewals [26] of SLIT. Issues related to treatment persistence are well known from chronic diseases requiring permanent and lifelong treatment. The 3-year treatment course applied to the AIT SLIT-tablet may benefit from strategies to improve patients' daily treatment adherence and long-term persistence interventions including communication and patient education as well as standardized follow-up visits [24].

About one third of patients diagnosed with AR only reported having bronchial symptoms at visit 1; of these the majority reported mild symptoms, and there was an overall improvement over time. Although the AR only

subgroup did not have a diagnosis of asthma, the data may suggest the importance of collecting the patient history of bronchial symptoms and carrying out objective assessments such as lung function tests regularly and bronchial provocation tests on suspicion, as misdiagnosis in asthma is known to occur [32].

Allergic patients may present with symptoms from the upper and lower airways, the eyes, and the skin. While moderate–severe respiratory symptoms underline a clear need for treating the cause of the HDM allergy, there may be concern clinically with inducing worsening of skin symptoms, for example. In this study, however, the number of patients reporting moderate to severe skin symptoms did not increase over time, and in general the allergic symptoms of the skin decreased. Also, as many as 51% had moderate to severe eye symptoms at visit 1, but only 10% at visit 3. This implies that symptoms other than respiratory symptoms due to HDM allergy appear to strengthen the indication for AIT rather than present as a concern for initiating treatment.

In this observational study, the number of patients who experienced symptom reductions (none, mild, moderate, or severe) by at least one level of severity was statistically significant in the total study population as well as for the subgroups. The symptom reductions were in turn reflected by statistically significant reductions in AR medication and inhaled corticosteroids after 1 year. The level of asthma symptom control was assessed according to GINA 2015 [8], and significant reductions in symptomatic medication was seen over time. Moreover, the data suggest that exploring of the allergic component in asthma is relevant and important.

The age criterion of this study was 18–-65 years, which was set to reflect the approved indication in the two countries of study conduct. The overall patient characteristics in this study closely reflect the RCTs of the SQ HDM SLIT-tablet conducted in adults [17, 19]. The median and mean age of patients herein was 37 years, with onset of allergic symptoms around 18 years of age, suggesting that patients in this study population predominantly had symptom debut as young adults.

LIMITATIONS

Due to the nature of the study as a non-interventional and observational study, a control group was not included, and further the study comprised a limited number of patients. Measures were not taken to assess treatment adherence. The study was designed to include three visits only, and this did not allow for a more detailed follow-up of patients. Further, the study lasted only for a year and did not allow for long-term evaluation of patient outcome. The level of asthma control was captured at all visits, but data are missing for one, four, and four patients at visits 1, 2, and 3, respectively.

CONCLUSION

The SQ HDM SLIT-tablet was safe and well tolerated in this observational study. Moreover, the type, frequency, and severity of AEs were comparable to what RCTs have previously demonstrated [17–19]. As explorative endpoints, statistically significant reductions in symptoms and medication use were seen in addition to improved asthma control after 1 year of treatment. Eighty-four percent of the patients completed this study of 1-year duration, but real-world studies in general point to the relevance and importance of careful patient education and close follow-up of long-term treatment to improve treatment adherence and long-term persistence, and in turn improve patient outcome.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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