

DR. KRISTIAN FUNDING ANDERSEN (Orcid ID : 0000-0002-7236-2612)

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**TITLE: CLINICAL BENEFITS OF TREATMENT WITH SQ HOUSE DUST MITE
SUBLINGUAL TABLET IN HOUSE DUST MITE ALLERGIC RHINITIS**

Short title: Clinical benefits with SQ HDM SLIT-tablet in HDM AR

Authors:

Pascal Demoly, MD, PhD, Department of Pulmonology, Division of Allergy, Hopital Arnaud de Villeneuve, University Hospital of Montpellier, and Sorbonne Universités, UPMC Paris 06, UMR-S 1136 INSERM, IPLESP, Equipe EPAR, 75013, Paris, France

Jörg Kleine-Tebbe, MD, Allergy & Asthma Center Westend, Outpatient Clinic & Research Center Hanf, Ackermann & Kleine-Tebbe, Berlin

Dorte Rehm, PhD, ALK, Hørsholm

Contact author following publication:

Pascal Demoly, Hopital Arnaud de Villeneuve, CHU de Montpellier, 191 avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 5;

Tel: +33 467336117 ; Email : pascal.demoly@inserm.fr

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Contact during submission and revision process :

Kristian Funding Andersen, PhD, ALK, Boege Alle 1, DK-2970 Hoersholm, Denmark.

Tel: +45 25676926; Email: kfadk@alk.net

(have provided Medical writer services on behalf of ALK, including assisting in drafting the manuscript, managing correspondence and editing based on author's reviews/comments, and manuscript submission)

Capsule summary:

Treatment with SQ house dust mite sublingual tablet for 1 year resulted in a decreased probability of having an allergic rhinitis exacerbation day (from 11% (placebo) to 5% (SQ house dust mite sublingual tablet)) and an increased probability of having a mild allergic rhinitis day (from 16% (placebo) to 34% (SQ house dust mite sublingual tablet)).

Keywords:

Allergy immunotherapy, SQ HDM SLIT-tablet, allergic rhinitis, house dust mite, clinical relevance.

Brief communication:

Respiratory allergy is caused by a hypersensitivity of the immune system that may lead to different clinical manifestations such as allergic rhinitis (AR), allergic asthma (AA), allergic conjunctivitis as well as atopic eczema (1). House dust mite (HDM) allergy classifies as a perennial allergy and most patients have persistent symptoms all year with different intensity due to variations in exposure over the year (2). In Europe, the prevalence of adult subjects with AR ranges from 17% to 29%, with an estimated overall prevalence of 22% corresponding to 53 million people affected (3). The frequency of HDM sensitization detected by specific immunoglobulin (Ig) E in those patients is 49%. A proportion of patients with AR are inadequately controlled by allergy pharmacotherapy (4), even when the treatment is guided by a physician. Furthermore, up to half of HDM AR patients also suffers from asthma (5;6).

Allergy immunotherapy (AIT) is a treatment option for allergy that is complementary to pharmacotherapy and allergen avoidance. AIT modulates the underlying immunologic mechanisms of the allergic disease and is the only known treatment with the potential to provide long-term, post-treatment benefits and altering the natural course of allergic diseases (2).

Though AIT has been used in allergy treatment for well over 100 years now, it is not until the last decade or two that the evidence base for this treatment modality has been consolidated through large-scale randomized, double-blind, placebo-controlled clinical trials. The traditional method for administering AIT treatment is through subcutaneous injections. Drop-based AIT was introduced

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during the 1990ies and sublingual (SLIT) tablets emerged a decade or so later. Currently, the most well documented AIT products are the SLIT-tablets, and their use has gradually been accepted and incorporated into international and national AIT practice guidelines (7). Pivotal clinical trials focus on demonstrating effect on a combination of symptom score and medication use (8). This approach is supported by regulatory agencies worldwide; however, a decrease in symptom score or medication use may be difficult to translate into meaningful clinical improvement. Therefore it is useful to convert symptom/medication scores into a more meaningful clinical term, such as exacerbation days and mild days. The results reported below are an attempt at such a conversion.

The SQ HDM SLIT-tablet is a fast-dissolving once-daily sublingual allergy immunotherapy tablet (oral lyophilisate) suitable for home treatment (once the first tablet has been tolerated under medical supervision), containing highly standardized *D. pteronyssinus*/*D. farinae* 1:1 allergen extract. The SQ HDM SLIT-tablet is indicated for the treatment of both HDM AR and HDM AA with associated AR in patients not well controlled by pharmacotherapy. The SQ HDM SLIT-tablet has demonstrated clinical benefit in both HDM AR and HDM AA (9;10). The phase 3 trial, EudraCT number 2011-002277-38, investigating the efficacy of the SQ HDM SLIT-tablet in HDM AR met the primary endpoint measured as total combined rhinitis score (TCRS) and has previously been reported in detail, including CONSORT diagram, patient disposition, primary and key secondary endpoints (9). Briefly, 1425 patients were screened for the trial and 992 were included. Co-sensitisations were frequent with 41% of patients being sensitized to grass, 41% to cat and 28% to dog with no difference between the treatment groups. In the trial, patients scored a total of 6 allergic symptoms, 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose), and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) on a scale from 0 to 3 (i.e. no to severe symptoms). The use of anti-allergic pharmacotherapy was also recorded by each patient and compiled into a medication score. Efficacy was evaluated during the last 8 weeks of the 1 year treatment period. The timing of randomization and start of baseline evaluation period and efficacy evaluation period were identical for the treatment groups, with baseline period starting for 50% of patients from 9 January to 15 February (100% of patients between 1 November to 5 March) and efficacy evaluation period starting for 50% of patients from 24 November to 8 January (100% of patients between 2 October to 12 March).

The post hoc results reported here concern only the 12 SQ-HDM dose since this is the dose that has obtained regulatory approval in a number of European countries and is being marketed (as ACARIZAX®/ACCARIZAX®). Results reported here include two measures that are directly related to the clinical relevance of the treatment effect found in the trial, i.e. probability of rhinitis exacerbation days and probability of having mild days. An AR exacerbation day was defined as a day with an AR symptoms score of 6 or of 5 with one individual symptom scored 3 (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping). This definition corresponds to the level of symptoms required for entering the trial. A mild day was defined as a day with no individual symptom scored higher than 1 (clearly present but minimal awareness, easily tolerated) and no antihistamine use; i.e. a day with no more than minimal awareness of the patient's HDM AR.

During the 8 week efficacy assessment period the probability of having an AR exacerbation for patients in the placebo group was 11% while the corresponding probability in the SQ HDM SLIT-tablet group was 5% (Figure 1; $p < 0.001$). Furthermore, for patients in the placebo group the

probability of having a mild rhinitis day during the 8 week efficacy assessment period was 16% while the corresponding probability in the SQ HDM SLIT-tablet group was 34% (Figure 1; $p<0.001$).

A responder analysis based on rhinitis exacerbations and mild days was performed (Table 1). An AR exacerbation responder was defined as a patient with no AR exacerbations during the 8 week efficacy evaluation period (AR exacerbations were defined as described above). At inclusion, all subjects (100%) in both groups experienced AR exacerbations (according to inclusion criteria). After 1 year of treatment 28% of the patients in the placebo group had no days with rhinitis exacerbation during the 8 weeks efficacy evaluation period versus 39% of patients in the SQ HDM SLIT-tablet group (Odds ratio: 1.64; $p=0.006$).

A mild day responder was defined as a patient experiencing 80% or more of days in the efficacy evaluation period as mild days. The percentage of patients in each group having $\geq 80\%$ mild days during the 8 week efficacy evaluation period was 17% in the placebo group versus 31% in the SQ HDM SLIT-tablet group ($p<0.001$). Thus, the number needed to treat (NNT) was 7.4, 95% CI [4.9;15.0] based on the above definition of responders.

The reduced probability of rhinitis exacerbations and increase in mild days reported here show that significantly better effects were found in tangible clinically relevant parameters in favor of SQ HDM SLIT-tablet treated patients over placebo. These benefits were demonstrated on top of the free access to allergy pharmacotherapy given to all patients in the trial under physician guidance. Importantly, the SQ HDM SLIT-tablet treated patients had, in addition to their improvements on AR symptoms, also a significant drop in allergy pharmacotherapy use (9). This supports that SQ HDM SLIT-tablet provides an underlying protection leading to improved control of the HDM respiratory allergic disease. The SQ HDM SLIT-tablet represents an add-on treatment for patients that are not well-controlled on allergy pharmacotherapy. Apart from improved effect on symptoms and a reduced need for anti-allergic pharmacotherapy in both HDM AR and AA, treatment with the SQ HDM SLIT-tablet reduced the probability of rhinitis exacerbations and increased the probability of patients having AR mild days. Both these measures are easy to understand for individual patients and the clinical effect they document will help improve the daily life of HDM AR sufferers.

Authors contributions:

Substantial contributions to the conception or design of the work: PD, JKT, DRE

The acquisition, analysis, or interpretation of data for the work: PD, JKT, DRE

Critical revisions for important intellectual content: PD, JKT, DRE

Final approval of the version to be published: PD, JKT, DRE

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: PD, JKT, DRE

Assistance with drafting, editorial changes and journal submission was provided by Dr. Kristian Funding Andersen of ALK

Conflict of interest statement:

PD has received consultancy fees from ALK, Stallergenes Greer, Circassia, Meda and Menarini; and is on the advisory board of Chiesi, AstraZeneca and ThermoFisher Scientific. JKT has received consultancy fees from Merck and Circassia; and is on the advisory board of ALK, Novartis, Leti and Bencard; has received grants from Circassia, Leti and Stallergenes Greer; has received payment for lectures from Allergopharma, ALK, Bencard, HAL Allergy, Leti, Lofarma, Novartis and Stallergenes Greer. DRE is an employee of ALK.

Pascal Demoly, MD, PhD, Department of Pulmonology, Division of Allergy, Hopital Arnaud de Villeneuve, University Hospital of Montpellier, Paris, France

Jörg Kleine-Tebbe, MD, Allergy & Asthma Center Westend, Outpatient Clinic & Clinical Research Center, Berlin, Germany

Dorte Rehm, PhD, ALK, Hørsholm, Denmark

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Table 1: Responder analysis

	N	Estimate	95% CI	p-value
AR exacerbation-free responders^a				
Placebo (% patients)	298	27.9%	[22.8;33.3]	
12 SQ-HDM (% patients)	284	38.7%	[33.0;44.7]	
Odds Ratio: 12 SQ-HDM vs. Placebo		1.64	[1.14;2.36]	0.006
Responders having ≥80% mild days^b				
Placebo (% patients)	298	17.1%	[13.0;21.9]	
12 SQ-HDM (% patients)	284	30.6%	[25.3;36.4]	
Odds Ratio: 12 SQ-HDM vs. Placebo		2.14	[1.42; 3.24]	<0.001

Evaluated during the end-of-trial efficacy evaluation period. N = number of patients included in the analysis;

CI = confidence interval. a: An AR exacerbation was defined as an AR symptoms score of 6 or of 5 with one individual symptom scored 3 (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping). b: A mild day was defined as a day with no individual

symptom scored higher than 1 (clearly present but minimal awareness, easily tolerated) and no antihistamine use.

Figure 1: Probability of having an AR exacerbation day or a mild AR day for Placebo and SQ HDM SLIT-tablet treated patients during the 8 week efficacy evaluation period.

Figure 1

