Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis

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Background: Preliminary studies have suggested the efficacy of sublingual tablets of house dust mite (HDM) extracts in adults with allergic rhinitis.

Objectives: We sought to assess the efficacy and safety of 2 doses of HDM sublingual tablets over 1 treatment year and the subsequent immunotherapy-free year.

Methods: Adults with HDM-associated allergic rhinitis were randomized in a double-blind, placebo-controlled study to receive 500 index of reactivity (IR) tablets, 300IR tablets, or placebo administered once daily for 1 year and were followed for the subsequent year. The primary efficacy variable was the Average Adjusted Symptom Score over the year 1 primary period (ie, October 1 to December 31). Symptoms and rescue medication scores, onset of action, patient-reported outcomes, and safety were secondary variables. The same end points were evaluated during the immunotherapy-free year. The primary efficacy end point was analyzed by using analysis of covariance.

Results: Five hundred nine participants were randomized, and 427 continued in the immunotherapy-free year. Both the 500IR and 300IR HDM sublingual tablets significantly reduced mean Average Adjusted Symptom Scores compared with placebo by −20.2% ($P = .0066$) and −17.9% ($P = .0150$), respectively. Efficacy of both doses was maintained during the treatment-free follow-up phase. The onset of action was at 4 months. Participants' global evaluation of treatment success was significantly higher in the 500IR and 300IR groups compared with the placebo group ($P = .0206$ and $P = .0001$, respectively). Adverse events were generally application-site reactions. There were no reports of anaphylaxis.

Conclusions: Twelve months of treatment with 500IR and 300IR sublingual tablets of HDM allergen extracts was efficacious and well tolerated. Efficacy was maintained during the treatment-free follow-up year. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Allergic rhinitis, double-blind, placebo-controlled, sublingual immunotherapy tablets, house dust mite*

Allergic rhinitis (AR) affects approximately 10% to 30% of the adult population and up to 40% of children and is associated with comorbidities, including asthma and sinusitis, as well as deteriorated quality of life and sleep disorders.[1-3] Patients with AR, whether seasonal or perennial, are at a higher risk of developing asthma than those in the general population.[4,5] Moreover, the risk of developing asthma is approximately 6 times higher in patients with allergy to house dust mites (HDMs) than those allergic to pollens.[6]

Patients in whom symptomatic treatments are ineffective or poorly tolerated or who want to reduce the long-term use of medications are candidates for allergen immunotherapy (AIT).[7] In clinical trials, subcutaneous and sublingual immunotherapy have both been shown to significantly reduce AR symptoms and the requirement for rescue medications.[8,9] Moreover, the benefits of AIT have been shown to persist after discontinuation.[10-12]

HDMs are one of the most common sources of indoor allergens and trigger perennial AR and asthma. The 2 main species are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.[13] The use of AIT with sublingual solutions of HDM extracts has shown benefit in adults and children with HDM-related rhinitis.[9] Clinical trials adhering to the most recent recommendations are still needed.[14,15]

Phase I study results showed that doses of HDM sublingual tablets up to 500 index of reactivity (IR) were well tolerated.[16] The purpose of this study was to evaluate the efficacy and safety of 2 doses of sublingual tablets of HDM allergen extracts compared with placebo in adults with HDM-associated AR.

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Supported by Stallergenes S.A.

Disclosure of potential conflict of interest: K.-C.B. has received honoraria for lectures from ALK-Abelló Arzneimittel GmbH, Bencard Allergie GmbH, Chiesi GmbH, and Novartis Pharma Arzneimittel GmbH; travel support from Mundipharma GmbH; and reimbursements for travel and data monitoring boards from Stallergenes. P.D. is a consultant (and a speaker) for Stallergenes, ALK-Abelló, Circassia, and Chiesi and was a speaker for Allergopharma, Merck, AstraZeneca, Menarini, and GlaxoSmithKline in 2010-2012, and was an investigator for Stallergenes and ALK-Abelló during the same period. M.W. has received honoraria from Stallergenes, ALK and Allergopharma and has served on advisory boards for Stallergenes. W.J.F. has served as a consultant for and received payment to her institution for providing expert testimony and studies on behalf of Stallergenes, GlaxoSmithKline, HAL Allergy, Merk Sharp & Dohme, and Optinose UK and BioInspire Technologies; has received book royalties from Elsevier and Thieme; and has received payment to her institution for development of educational presentations from Merk Sharp & Dohme. T.C. was a speaker for Allergopharma. A.I.T. has received payments for lectures for Stallergenes, ALK-Abelló, and Novartis. H.N., A.M., and R.K.Z. are employees of Stallergenes.

Received for publication February 14, 2013; revised November 8, 2013; accepted for publication November 18, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.11.012

Abbreviations used
AAdSS: Average Adjusted Symptom Score
AdSS: Adjusted Symptom Score
AIT: Allergen immunotherapy
AR: Allergic rhinitis
ARMS: Average Rescue Medication Score
ARSS: Average Rhinitis Symptom Score
ARTSS: Average Rhinitis Total Symptom Score
FAS: Full analysis set
HDM: House dust mite
IR: Index of reactivity
RMS: Rescue Medication Score
RTSS: Rhinitis Total Symptom Score
SPT: Skin prick test
TEAE: Treatment-emergent adverse event

METHODS

Study design

The study was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 48 centers in 7 European countries (ClinicalTrials.gov no. NCT00674700). The study complied with International Conference on Harmonisation Good Clinical Practice guidelines and was approved by the local regulatory authorities and independent ethics committees.

Participants were enrolled between October 2007 and February 2008 for 1 year of treatment and 1 year of follow-up. Using a computer-generated randomization list (block size of 6; for details on randomization, see the Methods section in this article's Online Repository at www.jacionline.org), eligible participants were randomized 1:1:1 to receive placebo or active treatment with HDM extracts at doses (expressed in IR, the in-house standardization unit) of 500IR or 300IR. Participants, investigators, and all other study personnel remained blinded for the entire study.

Participants

The study enrolled men and women age 18 to 50 years with a clinical diagnosis of moderate-to-severe HDM-associated AR for at least 1 year, a positive skin prick test (SPT) response to *D pteronyssinus* or *D farinae* (wheal diameter >3 mm; Stallergenes S.A., Antony, France), serum IgE specific for *D pteronyssinus* or *D farinae* of 0.7 kU/L or greater, and a baseline Average Rhinitis Total Symptom Score (ARTSS; scale, 0-12) of 5 or greater during a 7-day recording of 4 rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus, and nasal congestion) scored on a 0- to 3-point scale (absent, mild, moderate, or severe).[17]

Participants were excluded from the study if they had cosensitizations detected from SPTs with a panel of seasonal and perennial aeroallergens (birch, hazel, alder, olive, cypress, plane, 5-grass mix, mugwort, ragweed, *Alternaria* species, *Parietaria* species, cat, dog, cockroach *Cladosporium* species and *Aspergillus* species), leading to clinically relevant symptoms, sensitization, and home exposure to cat or dog allergens; an existing nasal condition that could confound efficacy and safety evaluations; asthma requiring treatment other than short-acting inhaled β_2-agonists; treatment with systemic oral, nasal, or inhaled steroids within 4 weeks before screening or with long-acting systemic steroids within 12 weeks before screening; FEV_1 less than 80% of predicted value; HDM immunotherapy in the last 10 years; or ongoing AIT treatment with any allergen.

Study treatment and rescue medication

Active treatment consisted of sublingual AIT tablets containing a 1:1 mixture of standardized extracts of both *D pteronyssinus* and *D farinae*. The allergen content of the study tablets measured with a commercial ELISA kit (INDOOR Biotechnologies, Charlottesville, Va) was 28 μg of Der p 1 and 120 μg of Der f 1 for the 500IR tablet and 16 μg of Der p 1 and 68 μg of Der f 1 for the 300IR tablet. To ensure blinding, the investigational products were matched for the number of tablets per treatment box, as well as for the size, shape, color, and taste of the tablets. Participants were instructed to leave the tablet under the tongue until it had completely dissolved before swallowing.

Participants took the first dose of treatment at the study site and were monitored for 30 minutes. The remainder of the treatment was taken at home. Treatment was initiated with a dose-escalation phase. Those in the 300IR group took 100IR on day 1, 200IR on day 2, and 300IR on day 3. Those in the 500IR group took 100IR on days 1 and 2, 200IR on days 3 and 4, 300IR on days 5 and 6, 400IR on days 7 and 8, and 500IR on day 9. Participants then entered a maintenance phase during which they took 1 sublingual tablet daily for the first year of the study. Tablets were to be taken at the same time every day from the randomization visit to the end of the treatment period.

Rescue medications (oral and ophthalmic antihistamines and nasal corticosteroids) were provided to participants, who were instructed to use them according to a stepwise regimen (see below) for the management of severe or intolerable AR symptoms. If participants remained symptomatic despite these treatments, they were to consult the investigator and were provided with oral corticosteroids, if necessary.

Assessments

During the assessment periods, participants were advised to record the occurrence and severity of 5 individual rhinoconjunctivitis symptom scores (sneezing, rhinorrhea, nasal pruritus, nasal congestion, and ocular itching) and use of rescue medication over the previous 24 hours. Diaries were to be completed by using a 4-point descriptor scale from 0 (absent) to 3 (severe) for each symptom. Participant-reported outcomes included a global evaluation of the efficacy of the sublingual tablets at month 12 by using a 5-point Likert scale (from marked worsening to marked improvement) and noted relative to the previous year. Treatment success was defined by a score of 4 ("slight to moderate improvement") or 5 ("marked improvement").

D pteronyssinus– and *D farinae*–specific serum IgE and IgG_4 levels were measured with the ImmunoCAP 250 (Thermo Scientific, Waltham, Mass) and the Immulite 2000 Immunoassay System (Siemens, Munich, Germany), respectively, at study entry and at months 12 and 24.

After SPTs for *D pteronyssinus* and *D farinae*, wheals were outlined and a print was made with transparent tape before shipment for central reading. The wheal diameters were then numerized by using an Epson Perfection V200 Photo scanner and measured with VISILOG 6.4 software (Noesis, Versailles, France). Diameters were derived from the following formula:

$$\text{Surface} = \pi \times \text{radius}^2.$$

Safety variables were adverse events (AEs) monitored throughout the study and categorized according to MedDRA (version 10.1) and data from physical examinations and clinical laboratory assessments.

Periods of evaluation

Participants completed their symptoms and rescue medication diaries at periods defined by their study visit dates. For the efficacy analysis, a primary period from October 1 to December 31 of each study year was defined to assess all participants during the same period of the year.[17] Diary data over 14 days after each visit were analyzed to assess the treatment onset of action, with the exception of each end-of-year visit (months 12 and 24), for which data over the 14 days preceding the visits were used (Fig 1).

Outcomes

The sum of the 4 rhinitis symptom scores defined the daily Rhinitis Total Symptom Score (RTSS; range, 0-12); ocular itching was analyzed independently. The daily Rescue Medication Score (RMS; range, 0-3) was derived as follows: 0, no rescue medication taken; 1, use of antihistamines (oral, ophthalmic, or both); 2, use of nasal corticosteroids; or 3, use of oral