

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

Karl-Christian Bergmann, MD,^a Pascal Demoly, MD, PhD,^b Margitta Worm, MD,^a Wytske J. Fokkens, MD, PhD,^c Teresa Carrillo, MD, PhD,^d Ana I. Tabar, MD, PhD,^e Hélène Nguyen, PharmD,^f Armelle Montagut,^f and Robert K. Zeldin, MD^f Berlin, Germany, Montpellier and Antony, France, Amsterdam, The Netherlands, and Las Palmas de Gran Canaria and Pamplona, Spain

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 2014;133:1608-14.)

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.

From ^aAllergy-Centre-Charité, Charité-Universitätsmedizin Berlin; ^bAllergology Department, CHU Montpellier; ^cAcademic Medical Centre, Otorhinolaryngology, Amsterdam; ^dAllergology Department, Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria; ^ethe Department of Allergy, Complejo Hospitalario de Navarra, Pamplona; and ^fStallergenes S.A., Antony.

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.

Available online December 31, 2013.

Corresponding author: Karl-Christian Bergmann, MD, Allergy-Centre-Charité, Department of Dermatology and Allergy, Campus Mitte, Charité-Universitätsmedizin Berlin, Luisenstraße 2-5, 10117 Berlin, Germany. E-mail: karlchristianbergmann@googlemail.com.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

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; FEV₁ 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 μ g of Der p 1 and 120 μ g of Der f 1 for the 500IR tablet and 16 μ g of Der p 1 and 68 μ g 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 IgG₄ 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

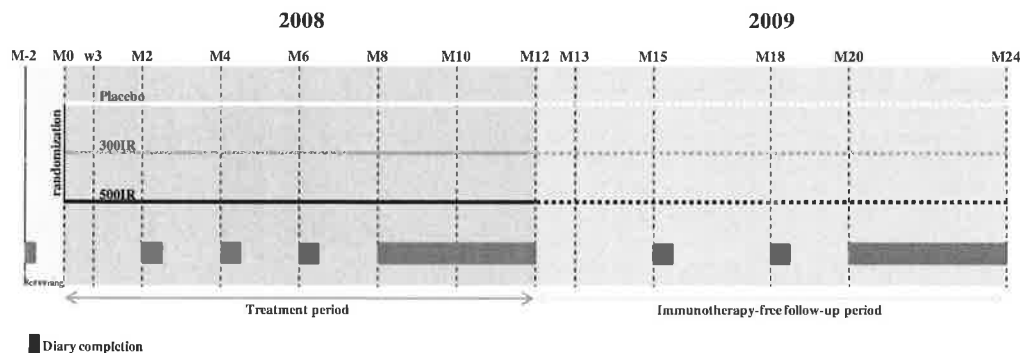


FIG 1. Study design. Participants recorded the occurrence and severity of their symptoms and use of rescue medications during screening (7 days) and once randomized at months 2, 4, 6, 15, and 18 (14 days) and during the primary periods (months 8-12 and months 20-24). Primary periods were defined from October 1 to December 31 of each study year.

corticosteroids. If more than 1 class of rescue medication was used on a particular day, the highest score was retained for the RMS of that day.

The primary efficacy variable was the Average Adjusted Symptom Score (AAdSS; range, 0-12) during the year 1 primary period. The AAdSS is subject specific and calculated as the average of daily Adjusted Symptom Scores (AdSSs) over the evaluation period. The daily AdSS (range, 0-12) is a score adjusting the daily RTSS for rescue medication use. The RTSS was adjusted as follows: if the participant took rescue medication on a given day, the AdSS equaled the RTSS of that day or the AdSS of the previous day, whichever was higher. The next day, the AdSS equaled the RTSS of that day or the AdSS of the day before, whichever was higher.¹⁸

Secondary efficacy variables included the average RTSS (ARTSS), individual average rhinitis symptom scores (ARSSs), the Average RMS (ARMS), and the patient's global evaluation of treatment efficacy.

Onset of action was defined as the first period during which the AAdSS of the actively treated group differed significantly from that of the placebo group and statistical significance was maintained for at least 2 consecutive periods.

As an exploratory objective, the efficacy and safety of HDM sublingual immunotherapy tablets continued to be monitored during a 12-month, treatment-free follow-up phase.

Statistical analyses

On the basis of results of prior studies of HDM sublingual drops,¹⁹ a sample size of 136 participants per treatment group would provide 80% power to detect a 0.87 mean difference in the AAdSS between active treatment and placebo, given an α value of .05 and a common SD of 2.5. Assuming a dropout rate of approximately 15%, randomization of 486 participants was planned (ie, 162 per treatment group).

Statistical analyses were performed with the SAS System, version 8.02 or higher (SAS Institute, Cary, NC). The threshold for statistical significance was set to a P value of less than .05, and all inferential tests were 2-sided.

The full analysis set (FAS) for year 1 (FAS_{Year1}) included all participants who received at least 1 dose of the investigational product and had at least 1 AdSS evaluation in the treatment year. The year 2 FAS (FAS_{Year2}) included all treated participants who had at least 1 AdSS evaluation during year 2.

The primary efficacy criterion was analyzed by using analysis of covariance, with treatment and pools of study centers as main effects and age, sex, asthma status, sensitization status (monosensitized vs polysensitized at baseline), and baseline ARTSS as covariates. Treatment comparison was done with a step-down approach for the primary end point (first 500IR vs placebo, then 300IR vs placebo, and then 500IR vs 300IR) to control the overall type I error rate at 5%.

ARTSSs, ARSSs, and ARMSs were analyzed as per the primary efficacy criterion. The treatment onset of action was analyzed by using a repeated-measures analysis of covariance mixed model. Global evaluation of treatment efficacy and treatment success was analyzed by using a row mean scores

Cochran Mantel-Haenszel test by using pooled center as a stratification variable. *D pteronyssinus* and *D farinae* SPT wheal diameters were analyzed as per the primary efficacy criterion, with the corresponding diameters at screening as the baseline covariate.

RESULTS

A total of 509 participants with HDM-associated AR were randomized to receive either 500IR ($n = 169$), 300IR ($n = 170$), or placebo ($n = 170$). Of these, 427 (84%) participants completed the treatment year, and 397 (78%) completed the 2 years of the study. FAS_{Year1} consisted of 466 participants; 43 participants did not have at least 1 AdSS during treatment. FAS_{Year2} consisted of 412 participants (the participant disposition is shown in Fig E1 in this article's Online Repository at www.jacionline.org).

At study entry, demographics and disease characteristics were similar across the 3 treatment groups (Table I). They remained so at the start of study year 2. Participants in FAS_{Year1} had a history of rhinitis for a mean of approximately 10 years. Approximately half (52%) were polysensitized, and 30% had intermittent asthma at study entry.

Overall treatment exposure in FAS_{Year1} averaged 353.1 days (SD, 50.61 days), with similar values across treatment groups.

Efficacy outcomes

Over the year 1 primary period, the AAdSS was significantly lower in the 500IR and 300IR groups compared with the placebo group (Table II). The relative difference versus placebo was 20.2% for the 500IR group and 17.9% for the 300IR group. There was no significant difference between the active groups. Presence of asthma and sensitization status did not affect the efficacy results.

The analysis of the ARTSS during the year 1 primary period was consistent with the AAdSS results (Fig 2, A). The least-squares mean ARMS, reflecting the consumption of rescue medication during the year 1 primary period, was less than 0.35 across groups, and differences were not significant (Fig 2, B). Compared with placebo, all of the individual symptom scores were lower in the active treatment groups, with statistical significance reached for sneezing, nasal pruritus, and ocular itching in the 500IR group and for sneezing, nasal pruritus, and nasal congestion in the 300IR group (Fig 2, C). For both active treatment groups, a significant

TABLE I. Baseline characteristics (FAS_{Year1})

	Placebo (n = 163)	300IR (n = 153)	500IR (n = 150)
Age (y)	30.0 (8.96)	29.0 (8.52)	30.1 (8.43)
Female sex, no. (%)	80 (49.1)	85 (55.6)	77 (51.3)
Duration of AR (y)	10.5 (8.49)	10.1 (8.62)	10.6 (8.57)
FEV ₁ (% predicted)	99.3 (13.04)	100.3 (11.01)	97.9 (13.44)
ARTSS*	6.79 (1.456)	6.94 (1.491)	7.26 (1.655)
Asthma	47 (28.8%)	49 (32.0%)	43 (28.7%)
Polysensitization†	88 (54.0%)	74 (48.4%)	82 (54.7%)

Results describing continuous variables are expressed as means (SDs). Results describing categorical variables are expressed as the number of participants and percentage relative to the number of participants in the FAS with nonmissing data. *ARTSS at baseline based on a 7-day daily record of the 4 rhinitis symptoms; no rescue medications were allowed.

†Sensitized to HDM allergen(s) and at least 1 other allergen tested.

TABLE II. AAdSS during the year 1 primary period (FAS_{Year1})

Treatment	No.*	LS mean (SE)
Placebo	153	3.87 (0.217)
300IR	141	3.18 (0.224)
500IR	136	3.09 (0.230)

Difference in LS means				
Comparison	Point estimate	95% CI	P value	Relative difference (%)
500IR vs placebo	-0.78	-1.34 to -0.22	.0066	-20.2
300IR vs placebo	-0.69	-1.25 to -0.14	.0150	-17.9
500IR vs 300IR	-0.09	-0.66 to 0.49	.7638	—

Statistical analysis was performed with analysis of covariance.

LS, Least-squares.

*Number of participants with data during the primary period and all covariates valid.

treatment effect on the primary efficacy variable was observed compared with placebo beginning at month 4. This was maintained through the end of the treatment year (Fig 3).

The patient's global evaluation of the efficacy of the treatment at end point for year 1 was significantly different in the 500IR and 300IR groups from that in the placebo group ($P = .0023$ and $P < .0001$, respectively). The proportion of participants who reported "marked improvement" was higher in the 500IR (33.1%) and 300IR (36.9%) groups than in the placebo group (18.0%). The frequency distribution for the patient's global evaluation of treatment efficacy is provided in Table E1 in this article's Online Repository at www.jacionline.org. There were also significant differences in treatment success for both active treatment groups (73.1% [$P = .0206$] for 500IR and 80.5% [$P = .0001$] for 300IR) compared with the placebo group (59.6%).

During the year 2 primary period, the significant reduction in AAdSSs observed in the active treatment groups compared with the placebo group during the year 1 primary period was maintained, with relative reductions of 19.1% in the 500IR group and 17.0% in the 300IR group compared with the placebo group (Fig 4, A). Similar reductions were observed in ARTSSs in the 2 active groups compared with the placebo group (Fig 4, B). There was no significant difference between the 2 active groups. As for the year 1 primary period, the use of rescue medication was low and the difference versus placebo was not statistically significant (Fig 4, C). All individual symptom scores were lower in the active groups compared with the placebo group (Fig 4, D).

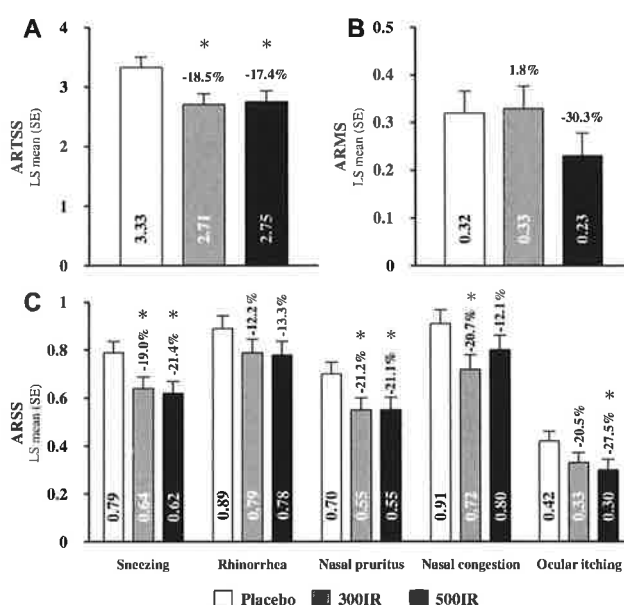


FIG 2. Symptom and rescue medication scores (FAS_{Year1}): ARTSS (A), ARMS (B), and ARSS (C). Observations for all variables were available for 136 participants in the 500IR group, 141 participants in the 300IR group, and 153 participants in the placebo group, except for ocular itching (131, 139, and 148 participants, respectively). * $P < .05$ (analysis of covariance, each of the 2 active groups vs the placebo group).

Serum immunologic outcomes

At study entry, *D pteronyssinus*- and *D farinae*-specific serum IgE and IgG₄ levels were similar across treatment groups. By months 12 and 24, there were no relevant changes in *D pteronyssinus*- and *D farinae*-specific serum IgE levels in any of the 3 treatment groups. Both *D pteronyssinus*- and *D farinae*-specific serum IgG₄ levels increased by 2- to 3-fold in the active treatment groups by the end of the treatment year and remained increased at the end of the follow-up year, whereas they remained essentially unchanged in the placebo group (see Fig E2 in this article's Online Repository at www.jacionline.org).

SPT wheal diameters

At the end of year 1, *D pteronyssinus* and *D farinae* mean wheal diameters were significantly reduced compared with those in the placebo group in the 500IR ($P = .0015$ and $P < .0001$, respectively) and 300IR ($P = .0022$ and $P = .0007$, respectively) groups. Mean wheal diameters were reduced relative to placebo by 13.4% and 17.6%, respectively, in the 500IR group and by 12.9% and 15.1%, respectively, in the 300IR group. Similar results were observed at the end of the immunotherapy-free follow-up year (see Table E2 in this article's Online Repository at www.jacionline.org).

Safety

The safety set included all participants who received at least 1 dose of the investigational product. Mean treatment exposure was 316 days (SD, 108.3 days) in the 500IR group, 324 days (SD, 100.4 days) in the 300IR group, and 345 days (SD, 73.6 days) in the placebo group.

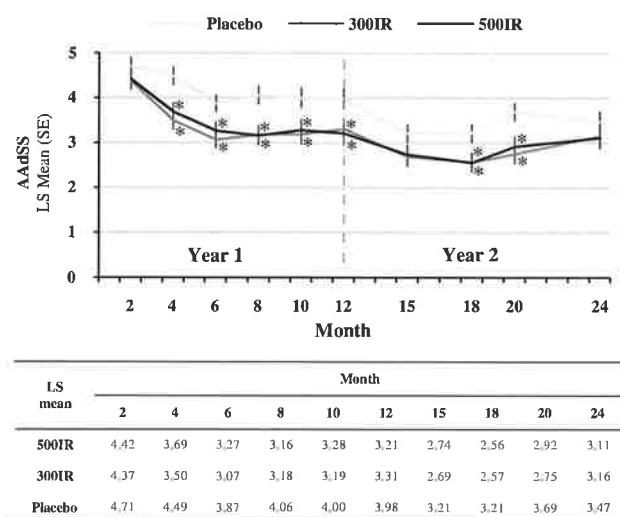


FIG 3. AAdSS (FAS_{Year1} and FAS_{Year2}). Fourteen-day diaries were collected after each time point visit (months 2-10 and months 15-20) or preceding the month 12 and month 24 visits. Mean baseline ARTSSs (no rescue medication allowed) were 7.26 (500IR group), 6.94 (300IR group), and 6.79 (placebo group). **P* < .05 (repeated-measures analysis of covariance mixed model, each of the 2 active groups vs the placebo group).

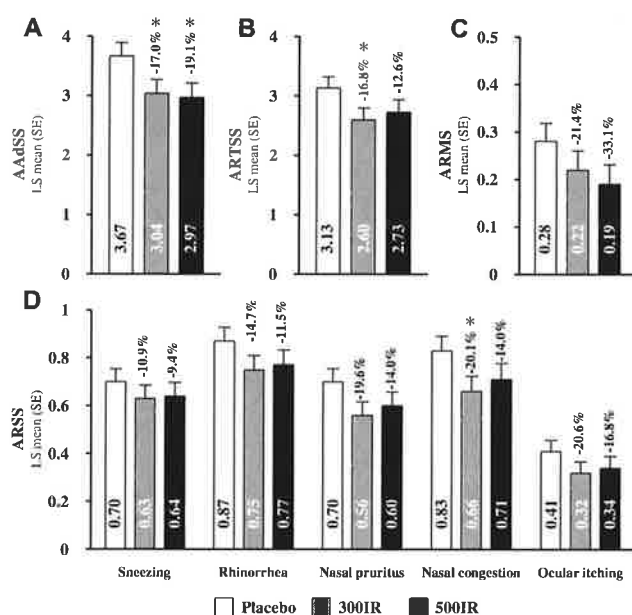


FIG 4. Symptom and rescue medication scores (FAS_{Year2}): AAdSS (A), ARTSS (B), ARMS (C) and ARSS (D). Observations for all variables were available for 120 participants in the 500IR group, 132 participants in the 300IR group, and 137 participants in the placebo group, except for ocular itching (117, 131, and 134 participants, respectively). **P* < .05 (analysis of covariance, each of the 2 active groups vs the placebo group).

No deaths occurred during the study, and there were no reports of anaphylactic shock or anaphylaxis. No participants received epinephrine.

Nine participants experienced serious treatment-emergent adverse events (TEAEs): 1 participant in the 500IR group (respiratory distress caused by sublingual edema and associated swallowing difficulties), 6 participants in the 300IR group

(metrorrhagia, vaginal laceration, pharyngeal edema, worsening of pre-existing eczema, tubo-ovarian abscess, and injury and road traffic accident [both in 1 participant]), and 2 participants in the placebo group (urticaria and pituitary tumor). Respiratory distress, pharyngeal edema, eczema, and urticaria were considered by the investigators to be related to treatment, and all but the participant reporting eczema were discontinued from the study.

The most commonly reported TEAEs in the active treatment groups were application-site reactions (ie, oral pruritus, throat irritation, and mouth edema; Table III) and were generally mild to moderate in intensity. More participants prematurely withdrew from the study because of TEAEs in the 500IR group (20 [11.8%] participants) and 300IR group (17 [10.0%] participants) than in the placebo group (5 [2.9%] participants), mainly for pharyngeal edema, dyspepsia, nausea, and mouth edema. Asthma, cough, dyspnea, and wheeze were reported as TEAEs by a similar percentage of participants in the active and placebo groups. No difference in the safety profile was observed between the groups receiving the 2 active doses.

During the immunotherapy-free year, none of the 8 serious posttreatment AEs reported by 5 participants in the active treatment groups were considered drug related. Similar proportions of participants reported posttreatment AEs in the 3 treatment groups (see Table E3 in this article's Online Repository at www.jacionline.org). No safety signal was observed.

DISCUSSION

This randomized, double-blind, placebo-controlled study is the first large-scale trial evaluating the efficacy of 500IR and 300IR HDM sublingual tablets in relieving HDM-associated AR symptoms. Active treatment resulted in a significant improvement in AAdSSs during the year 1 evaluation period. Efficacy persisted over the immunotherapy-free evaluation period. No significant differences between the active groups were observed for any of the efficacy end points.

Studies that investigated the efficacy of subcutaneous immunotherapy for HDM-associated rhinitis have consistently shown improvement in rhinitis symptoms.²⁰⁻²⁴ In a recent review of the use of sublingual immunotherapy for AR, a subgroup analysis of 9 double-blind, placebo-controlled studies of children and adults with HDM-associated AR (sample size range in the active treatment groups was 8-139 participants, with 8 of the 9 studies including fewer than 40 participants in the active treatment groups) was performed. This analysis confirmed the efficacy of sublingual immunotherapy for HDM-associated rhinitis.⁹ The present study is the largest to date specifically focused on assessing the efficacy of sublingual AIT for HDM-associated AR.

Onset of action was investigated as a secondary end point. It was defined as the first period during which the difference in AAdSSs between the active and placebo groups was significant and statistical significance was maintained for at least 2 consecutive time points. The treatment effect was significant beginning 4 months after treatment initiation and was maintained continuously over the treatment year.

Identifying a population whose symptoms are driven by a specific aeroallergen is a challenge in assessing the efficacy of immunotherapy. In this study a clinical history consistent with HDM-associated AR and confirmation by using positive SPTs and *in vitro* testing for HDM-specific serum IgE antibodies was

TABLE III. Incidence of TEAEs reported by at least 5% of participants in any group (Safety Set_{Year1})

System organ class, preferred term	Treatment year (year 1)		
	Placebo (n = 170), no. (%)	300IR (n = 170), no. (%)	500IR (n = 169), no. (%)
Participants with ≥1 TEAE	136 (80.0)	150 (88.2)	141 (83.4)
Gastrointestinal disorders	38 (22.4)	93 (54.7)	102 (60.4)
Oral pruritus	8 (4.7)	51 (30.0)	43 (25.4)
Mouth edema	1 (0.6)	21 (12.4)	28 (16.6)
Tongue edema	1 (0.6)	9 (5.3)	10 (5.9)
Lip edema	0 (0.0)	12 (7.1)	4 (2.4)
Infections and infestations	91 (53.5)	93 (54.7)	74 (43.8)
Nasopharyngitis	39 (22.9)	28 (16.5)	23 (13.6)
Influenza	16 (9.4)	15 (8.8)	14 (8.3)
Pharyngitis	19 (11.2)	17 (10.0)	10 (5.9)
Upper respiratory tract infection	9 (5.3)	11 (6.5)	5 (3.0)
Respiratory, thoracic, and mediastinal disorders	50 (29.4)	61 (35.9)	65 (38.5)
Throat irritation	7 (4.1)	42 (24.7)	36 (21.3)
Cough	18 (10.6)	7 (4.1)	16 (9.5)
Pharyngeal edema	0 (0.0)	6 (3.5)	11 (6.5)
Asthma	10 (5.9)	4 (2.4)	10 (5.9)
Pharyngolaryngeal pain	12 (7.1)	6 (3.5)	7 (4.1)
Dyspnea	6 (3.5)	9 (5.3)	2 (1.2)
Nervous system disorders	40 (23.5)	28 (16.5)	28 (16.6)
Headache	33 (19.4)	23 (13.5)	24 (14.2)
Skin and subcutaneous tissue disorders	22 (12.9)	13 (7.6)	21 (12.4)
Eczema	9 (5.3)	4 (2.4)	3 (1.8)
Ear and labyrinth disorders	6 (3.5)	8 (4.7)	15 (8.9)
Ear pruritus	1 (0.6)	4 (2.4)	13 (7.7)
Musculoskeletal and connective tissue disorders	18 (10.6)	12 (7.1)	12 (7.1)
Injury, poisoning, and procedural complications	8 (4.7)	9 (5.3)	9 (5.3)
General disorders and administration-site conditions	20 (11.8)	10 (5.9)	8 (4.7)
Pyrexia	10 (5.9)	4 (2.4)	1 (0.6)

AEs were classified according to their system organ class and preferred term (MedDRA version 10.1). TEAEs were AEs occurring during the treatment period up to 30 days after the last treatment administration.

no., Number of participants with at least 1 event in the given preferred term; %, percentage of participants with at least 1 event relative to the number of participants in each treatment group in the safety set.

required for inclusion. About half of randomized participants were polysensitized, a proportion reflective of the real-world experience.²⁵ Participants also had to have a baseline average rhinitis total symptom score of at least 5 of 12. Nevertheless, and consistent with the immunotherapy literature,²⁶ adjusted symptom scores in the placebo group decreased from a mean of approximately 7 at baseline (ie, without rescue medication) to less than 5 at the first visit after treatment initiation (ie, month 2) and less than 4 during the year 1 primary period. In this study the use of rescue medication was modest and not different in either of the 2 active treatment groups compared with placebo. A minimum threshold of rescue medication use was not an inclusion criterion. In future studies, further refinement of the inclusion criteria must be considered so as to enable the assessment of treatment efficacy.

In addition to their symptoms and use of rescue medications, participants provided a global evaluation of the treatment efficacy at the end of the treatment period. Of note, when treatment efficacy is assessed by the patient, a positive evaluation is not uncommon in the placebo group and does not reflect meaningful improvement.²⁶⁻²⁸ Significantly higher rates of success were reported by participants in the active treatment groups compared with the placebo group. This suggests that the reduction in symptoms reported by participants was perceived as a meaningful improvement.

Previous studies have suggested that the persistence of AIT efficacy is dependent on the length of the treatment period.²⁹ Treatment for 3 years is considered optimal to maintain a long-term, disease-modifying effect. In this study, because the primary end point was measured after 1 year of treatment, the duration of the immunotherapy-free period was fixed at 1 year on an exploratory basis. The efficacy demonstrated in this study and its persistence over the immunotherapy-free year support the evaluation of its sustained and posttreatment efficacy in future studies.

The favorable safety profile of 500IR and 300IR sublingual tablets of HDM allergen extracts was consistent with that observed in previous studies of sublingual immunotherapy.^{9,14,30-32} There were no reports of anaphylactic shock or anaphylaxis.

In conclusion, in this study of adults with HDM-associated AR, 12 months of treatment with 500IR and 300IR sublingual tablets of HDM allergen extracts was efficacious, with results favoring the 500IR dose. Treatment benefit was maintained during the subsequent immunotherapy-free year. There were no appreciable differences in tolerability between the active treatment groups.

We thank all VO57.07 study participants and site staff for their commitment to the study. We also acknowledge Marie-Pierre Furrer's contribution as medical writer.

Clinical implications: HDM sublingual tablets are effective and well tolerated in adults with HDM-associated AR. Efficacy was significant after 4 months of treatment and maintained in the subsequent immunotherapy-free year.

REFERENCES

- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63(Suppl 86):8-160.
- Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc* 2007;28:3-9.
- Pawankar R, Canonica G, Holgate S, Lockey R. WAO white book on allergy. Milwaukee (WI): World Allergy Organization; 2011.
- Rowe-Jones JM. The link between the nose and lung, perennial rhinitis and asthma—is it the same disease? *Allergy* 1997;52:20-8.
- Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. *Ann Allergy Asthma Immunol* 1999;82:296-305.
- Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;57:1048-52.
- Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(Suppl):S1-S55.
- Fernandez-Caldas E, Iraola V, Boquete M, Nieto A, Casanovas M. Mite immunotherapy. *Curr Allergy Asthma Rep* 2006;6:413-9.
- Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010;(12):CD002893.
- Canonica GW, Passalacqua G. Disease-modifying effect and economic implications of sublingual immunotherapy. *J Allergy Clin Immunol* 2011;127:44-5.
- Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;64(Suppl 91):1-59.
- Eifan AO, Shamji MH, Durham SR. Long-term clinical and immunological effects of allergen immunotherapy. *Curr Opin Allergy Clin Immunol* 2011;11:586-93.
- Mosbech H. House dust mite allergy. *Allergy* 1985;40:81-91.
- Casale TB, Canonica GW, Bousquet J, Cox L, Lockey R, Nelson HS, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;124:665-70.
- Bousquet PJ, Calderon MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. The Consolidated Standards of Reporting Trials (CONSORT) statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA2LEN) article. *J Allergy Clin Immunol* 2011; 127:49-56.e11.
- Demoly P, Meziane L, Le Gall M, André C, Melac M. Safety and tolerability of house dust mite tablets in sublingual immunotherapy. *J Allergy Clin Immunol* 2008;121(Suppl):S128.
- Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;62:317-24.
- Grouin JM, Vicaut E, Jean-Alphonse S, Demoly P, Wahn U, Didier A, et al. The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. *Clin Exp Allergy* 2011;41:1282-8.
- Guez S, Vatrinet C, Fadel R, André C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55:369-75.
- Solari JE, Loo J, Felices A, Casas J. Immunotherapy for patients with persistent allergic rhinitis unsatisfied with free chronic pharmacotherapy. *Allergol Immunopathol* 2006;34:102-6.
- Tahamiler R, Saritzali G, Canakcioglu S, Ozcora E, Dirican A. Comparison of the long-term efficacy of subcutaneous and sublingual immunotherapies in perennial rhinitis. *ORL J Otorhinolaryngol Relat Spec* 2008;70:144-50.
- Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol* 2012;157:288-98.
- Tabar AI, Echechipia S, Garcia BE, Olaguibel JM, Lizaso MT, Gomez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol* 2005; 116:109-18.
- Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceci NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy* 2010;40:922-32.
- Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758-64.
- del Cuvillo A, Sastre J, Bartra J, Mullol J, Davila I, Montoro J, et al. Placebo effect in clinical trials involving patients with allergic rhinitis. *J Investig Allergol Clin Immunol* 2011;21(Suppl 3):40-5.
- Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002;88:592-600.
- Meltzer E, Malmstrom K, Lu S, Prenner B, Wei L, Weinstein S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000;105:917-22.
- Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol* 2011;127:57-63, e1-3.
- Passalacqua G, Canonica GW. Sublingual immunotherapy for allergic respiratory diseases: efficacy and safety. *Immunol Allergy Clin North Am* 2011;31: 265-77.
- Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
- Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6.e3.

METHODS

Randomization

Eligible patients were randomized 1:1:1 to one of the 2 doses of active treatment or placebo by using a computer-generated list (block size of 6).

A randomization list was created by Quintiles South Africa with SAS System, version 8.2. Treatments were allocated chronologically with the next available treatment number in a consecutive and ascending way in the order of randomization.

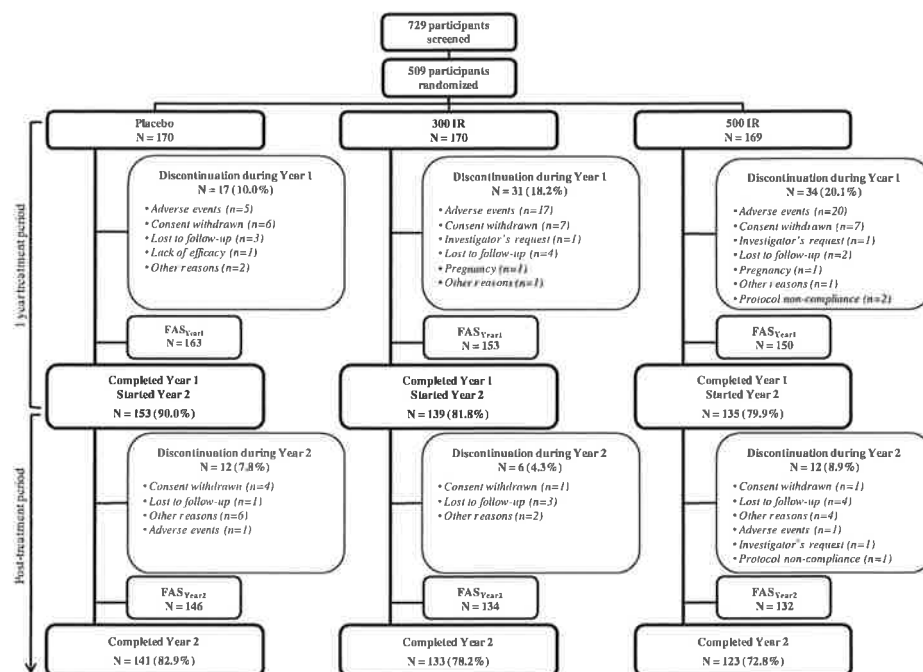


FIG E1. Participants' disposition. Participants were randomized to one of the 3 groups, treated for approximately 12 months, and followed for the subsequent 12-month, immunotherapy-free period. Safety set year 1 was comprised of all participants who received at least 1 dose of investigational product. Safety set year 2 was comprised of all participants who completed year 1.

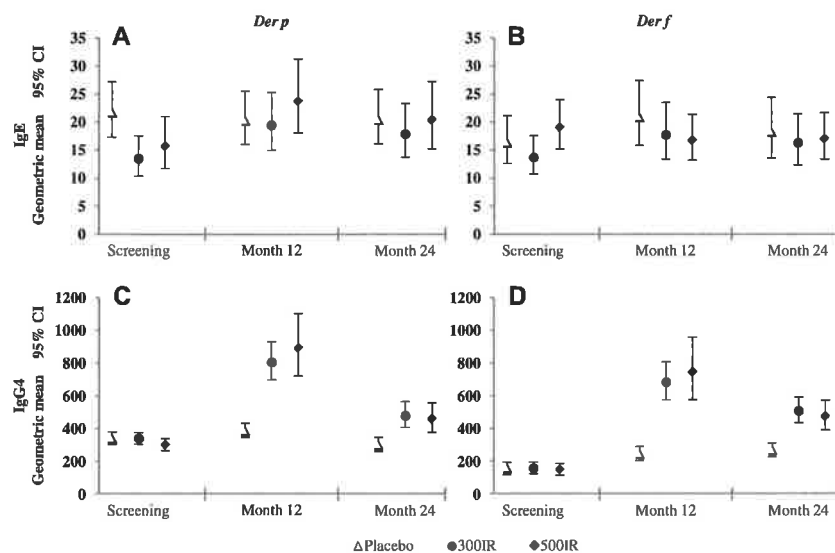


FIG E2. Immunologic markers (FAS_{Year2}). Serum specific IgE levels for *D pteronyssinus* (A) and *D farinae* (B) and serum specific IgG₄ levels for *D pteronyssinus* (C) and *D farinae* (D) at baseline, month 12, and month 24.

TABLE E1. Global evaluation of treatment efficacy by the patient (FAS_{Year1})

	Placebo (n = 161),* no. (%)	300IR (n = 149),* no. (%)	500IR (n = 145),* no. (%)
Marked worsening	4 (2.5%)	1 (0.7%)	1 (0.7%)
Slight to moderate worsening	7 (4.3%)	1 (0.7%)	5 (3.4%)
No change	54 (33.5%)	27 (18.1%)	33 (22.8%)
Slight to moderate improvement	67 (41.6%)	65 (43.6%)	58 (40.0%)
Marked improvement	29 (18.0%)	55 (36.9%)	48 (33.1%)

*Number of participants with global evaluation data.

TABLE E2. SPT mean wheal diameter (in millimeters) at end point (FAS_{Year1} and FAS_{Year2})

Year 1					
<i>D pteronyssinus</i>					
Treatment	No.	LS mean (SE)			
Placebo	156	6.48 (0.206)			
300IR	144	5.64 (0.211)			
500IR	141	5.61 (0.220)			
Difference in LS means					
Comparison	Point estimate	95% CI	P value	Relative difference (%)	
500IR vs placebo	−0.87	−1.40 to −0.33	.0015	−13.4	
300IR vs placebo	−0.84	−1.37 to −0.30	.0022	−12.9	
500IR vs 300IR	−0.03	−0.58 to 0.52	.9154		
<i>D farinae</i>					
Treatment	No.	LS mean (SE)			
Placebo	156	6.19 (0.208)			
300IR	144	5.26 (0.213)			
500IR	141	5.10 (0.222)			
Difference in LS means					
Comparison	Point estimate	95% CI	P value	Relative difference (%)	
500IR vs placebo	−1.09	−1.63 to −0.55	<.0001	−17.6	
300IR vs placebo	−0.94	−1.48 to −0.40	.0007	−15.1	
500IR vs 300IR	−0.15	−0.71 to 0.40	.5839		
Year 2					
<i>D pteronyssinus</i>					
Treatment	No.	LS mean (SE)			
Placebo	140	6.60 (0.204)			
300IR	130	6.05 (0.212)			
500IR	125	5.90 (0.217)			
Difference in LS means					
Comparison	Point estimate	95% CI	P value	Relative difference (%)	
500IR vs placebo	−0.70	−1.23 to −0.17	.0100	−10.6	
300IR vs placebo	−0.55	−1.08 to −0.02	.0412	−8.3	
500IR vs 300IR	−0.15	−0.69 to 0.39	.5901		
<i>D farinae</i>					
Treatment	No.	LS mean (SE)			
Placebo	140	6.27 (0.209)			
300IR	130	5.45 (0.217)			
500IR	125	5.59 (0.222)			
Difference in LS means					
Comparison	Point estimate	95% CI	P value	Relative difference (%)	
500IR vs placebo	−0.68	−1.22 to −0.14	.0140	−10.9	
300IR vs placebo	−0.82	−1.36 to −0.28	.0030	−13.1	
500IR vs 300IR	0.14	−0.41 to 0.69	.6182		

Statistical analysis was performed with analysis of covariance.

LS, Least-squares; No., number of participants with data during the primary period and all covariates valid.

TABLE E3. Incidence of posttreatment AEs reported by at least 5% of participants in any group (Safety Set_{Year2})

System organ class, preferred term	Immunotherapy-free year (year 2)		
	Placebo (n = 153), no. (%)	300IR (n = 139), no. (%)	500IR (n = 135), no. (%)
Participants with ≥ 1 PTAE	79 (51.6)	70 (50.4)	58 (43.0)
Infections and infestations	61 (39.9)	44 (31.7)	39 (28.9)
Nasopharyngitis	16 (10.5)	14 (10.1)	11 (8.1)
Influenza	9 (5.9)	2 (1.4)	5 (3.7)
Bronchitis	3 (2.0)	7 (5.0)	3 (2.2)
Upper respiratory tract infection	8 (5.2)	3 (2.2)	3 (2.2)
Respiratory, thoracic, and mediastinal disorders	20 (13.1)	16 (11.5)	12 (8.9)
Cough	8 (5.2)	7 (5.0)	2 (1.5)
Gastrointestinal disorders	9 (5.9)	13 (9.4)	11 (8.1)
Musculoskeletal and connective tissue disorders	10 (6.5)	7 (5.0)	8 (5.9)
Nervous system disorders	16 (10.5)	10 (7.2)	7 (5.2)
Headache	16 (10.5)	7 (5.0)	6 (4.4)

AEs were classified according to system organ class and preferred term (MedDRA version 10.1). Posttreatment adverse event (PTAEs) were AEs occurring at least 30 days after the last treatment administration.

no., Number of participants with at least 1 event in a given preferred term; %, percentage of participants with at least 1 event relative to the number of participants in each treatment group in the safety set.

