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Efficacy of house dust mite sublingual tablet in the treatment of allergic rhinoconjunctivitis: A randomized trial in a pediatric population

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Abstract

Background: The efficacy and safety of 300 index of reactivity (IR) tablets of house dust mite (HDM) allergen extracts in Japanese pediatric (5-16 years old) patients with allergic rhinitis (AR) were assessed in a double-blind, randomized, placebo-controlled study (JAPIC CTI-152981).

Methods: Patients were randomized 1:1 to HDM sublingual tablets or placebo once daily for 52 weeks. The primary end-point was average adjusted symptom score (AASS; average of daily Rhinitis Total Symptom Scores, comprising sneezing, rhinorrhea, nasal congestion, and nasal pruritus, adjusted for rescue medication use), analyzed during Weeks 48-52 (mixed-effects model for repeated measures).

Results: Of 438 patients randomized, 403 (92%; 193 active, 210 placebo) completed the study. AASS (least-squares [LS] mean [SE]) during Weeks 48-52 was significantly ($P = 0.0005$) lower in the active group compared with placebo (6.32 [0.20] vs 7.27 [0.19]; relative LS mean difference, −13%). Immunological responses (IgE and IgG4 antibodies specific to antigens of two HDM species) were significantly greater in the active group compared with placebo ($P < 0.0001$). Almost all patients experienced mild or moderate adverse events (AEs). The most common treatment-related AEs were oral pruritus, mouth edema, throat irritation, and ear pruritus. One patient experienced serious pseudocroup (subglottic laryngitis) that recovered. There were no deaths or anaphylaxis requiring the use of injectable adrenaline.

Conclusions: The HDM tablet significantly improved symptoms of HDM-induced perennial AR and was associated with a significant immunological response. The safety profile in pediatric patients was consistent with that in adults, with no new safety concerns.

KEYWORDS

allergens: inhalative allergens, rhinitis: allergic, rhinitis: clinical trials, rhinitis: specific immunotherapy, SIT: SLIT

1 | INTRODUCTION

Allergic rhinitis (AR) is a type I allergic disease characterized by repetitive sneezing, watery rhinorrhea, pruritus, and nasal blockage. One common causative antigen is the house dust mite (HDM), for example, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* species.[1] Allergenic reactions in HDM allergy are related to the adaptive immune response, which depends on immunoglobulin E (IgE),[1] and allergen immunotherapy involves administration of a specific allergen to provide protection against allergic symptoms and inflammatory reactions in patients with IgE-mediated allergy.[1]

A sublingual tablet containing standardized allergen extracts from *D. pteronyssinus* and *D. farinae* in a total allergenic activity ratio (expressed as index of reactivity [IR]) of 1:1 has been developed.[2,3] Research has shown that the 300IR HDM tablet is effective and well tolerated in adult and adolescent patients aged 12 years and older with AR. In two double-blind, placebo-controlled studies in adults and adolescents with HDM-associated AR, 300IR HDM tablets significantly reduced mean average adjusted symptom scores (AASS) compared with placebo.[2,3] Although local allergic reactions occurred more frequently with active treatment than with placebo, the favorable safety profile of 300IR HDM tablets was confirmed.[2,3] In addition, the effectiveness of one year of treatment with 300IR HDM tablets was maintained for a subsequent year after ceasing treatment.[2] In Japan, HDM tablets were approved in March 2015 for "allergen immunotherapy for AR due to house dust mites" in adults and adolescents ≥12 years of age (Actair® Sublingual Tablets 100 Units [IR] and 300 Units [IR] for HDM, Stallergenes Greer). In addition, HDM sublingual immunotherapy was added to the 2017 Japanese[1] and the 2015 US[4] AR guidelines, leading to its recognition as a treatment option for AR.

According to a survey in 2002, the prevalence of AR in elementary students across 11 prefectures in western Japan was 20.5%.[5] Because of the common underlying cellular processes, AR in children is a risk factor for subsequent development of allergic airways diseases, including asthma.[6] Allergen immunotherapy provides protection against allergic symptoms that is not limited to AR[7] and may prevent additional allergies and asthma from developing.[6] Therefore, it is important to start allergen immunotherapy for AR in young children.[6] However, the efficacy, safety, and immunological response of HDM tablets in pediatric patients have not yet been demonstrated.

The aim of this double-blind, randomized, placebo-controlled study was to assess the efficacy, safety, and immunological response of standardized HDM allergen extract tablets in pediatric (≥5 and ≤16 years old) patients with perennial AR.

2 | METHODS

This multicenter, double-blind, randomized, placebo-controlled study was conducted at 51 medical institutions throughout Japan between October 2015 and December 2016. The protocol, informed assent form, and informed consent form/written information were approved by the ethics committee of Shionogi & Co., Ltd. and the institutional review board of each study site, and the study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Written informed consent or assent was obtained from legal representatives of patients (consent), patients aged ≥7 and ≤11 years, if possible (assent), patients aged ≥12 years (consent or assent), and patients aged 16 years (consent). The study is registered at National Institute of Public Health Clinical Trials Search (https://rctportal.niph.go.jp/en/, JAPIC CTI-152981).

2.1 | Study design and treatment protocol

The study comprised a screening period (up to 24 weeks before enrollment), a 2-week pretreatment observation period, a 52-week treatment period, and a 1-week post-treatment observation period.

After the pretreatment observation period, patients were randomized (web-based system) 1:1 to receive placebo or HDM tablets (active) once daily by a statistical minimization method using the allocation factors of the average Rhinitis Total Symptom Score (RTSS), age, and IgE score. The dose of the HDM tablet was increased from 100IR (Day 1) to 200IR (Day 2) to the maintenance dose of 300IR (Day 3 to Week 52). All drugs were manufactured by Stallergenes Greer (Antony, France).

2.2 | Study population

The main inclusion criteria were as follows: male and female outpatients ≥5 and ≤16 years, AR symptoms for ≥2 years, a score of ≥3 on the quantitative analysis of IgE antibody specific to *D. pteronyssinus* and/or *D. farinae* antigens (ImmunoCAP® test, analyzed at BML, Inc, Kawagoe, Japan), positive nasal provocation test using allergen disk for house dust, and RTSS (0-4 for sneezing, rhinorrhea, and nasal congestion, and 0-3 for nasal pruritus; total 0-15 points; criteria for each symptom of RTSS are described in Supporting information) ≥6 points/d for 7 days before randomization.[3] The nasal provocation test was defined as positive if two or more signs of nasal mucosal swelling, watery rhinorrhea, and nasal symptoms, including nasal pruritus and/or sneezing, were increased in comparison with using a blank disk, as per the 2017 Japan AR guideline.[1] Patients were excluded from the study if suspected of symptomatic AR due to allergens other than HDM with specified ImmunoCAP® score for each allergen, had mild persistent or more severe asthma (because the safety profile of HDM tablets has not yet been confirmed in patients with asthma), or required inhaled corticosteroid treatment.

2.3 | End-points

The primary efficacy end-point was the AASS, defined as the average of daily RTSSs adjusted for the use of rescue medications (scale 0-15),[3,8] during Weeks 48-52 of treatment. Symptoms were

self-assessed by patients or guardians and recorded daily in the patient diary. Use of rescue medication was also recorded.

Additional efficacy end-points were as follows: average RTSS of Weeks 8-10, Weeks 16-18, Weeks 24-26, Weeks 32-34, Weeks 40-42, and Weeks 48-52 (ARTSS); Average Rescue Medication Score (ARMS),[3] the average of the Rescue Medication Score (RMS, 0-4) based on patient diary records[3]; Average Combined Score (ACS), the average of daily combined scores (calculated as [RTSS/4 + RMS]/2; range: 0-2.875); Individual Symptom Scores (ISSs) of the four nasal and two ocular symptoms (itchy and watery eyes); overall assessments by patients or their guardians; and general improvement as assessed by investigators.[1,3,7,8] Definitions of the efficacy scores are shown in the footnotes to Table 2. Investigators evaluated general improvement as marked worsening, slight to moderate worsening, no change, slight to moderate improvement, or marked improvement compared with baseline. Adherence was assessed by the investigator based on study drug tablets retrieved from patients or guardians.

At baseline and at Week 52 or discontinuation, mite antigen-specific IgE/IgG4 antibodies were analyzed at BML Inc, Kawagoe, Japan. Safety was assessed by the reporting of adverse events (AEs) and serious AEs (SAEs), coded using the Medical Dictionary for Regulatory Activities, version 18.0.

2.4 | Statistical analysis

A target sample size of 400 patients was set to provide 168 patients per group (15% withdrawal rate) and 90% power to detect a difference in means of −0.96 between groups, assuming a common SD of 2.7, using a Student's *t* test. The safety analysis population included all patients who received at least one dose of study treatment and were GCP-compliant. The efficacy analysis population (full analysis set) included all patients in the safety analysis population who were assessed for efficacy. Baseline was defined as the pretreatment observation period.

The primary efficacy analysis used a mixed-effects model for repeated measures (MMRM) approach that included all available AASS data at 6 scheduled timepoints (Weeks 8-10, Weeks 16-18, Weeks 24-26, Weeks 32-34, Weeks 40-42, and Weeks 48-52) as response variables; timepoint, treatment group, and treatment-by-timepoint interaction as fixed effects; and age, baseline AASS, and IgE scores ≥3 for spring pollen as covariates. Missing data were not imputed. Between-group differences were assessed using the least-squares (LS) means (standard error [SE]) estimated from the MMRM approach. Other scores were analyzed as per the primary variable. Improvement rate of the overall assessment was compared between treatment groups using Fisher's exact test.

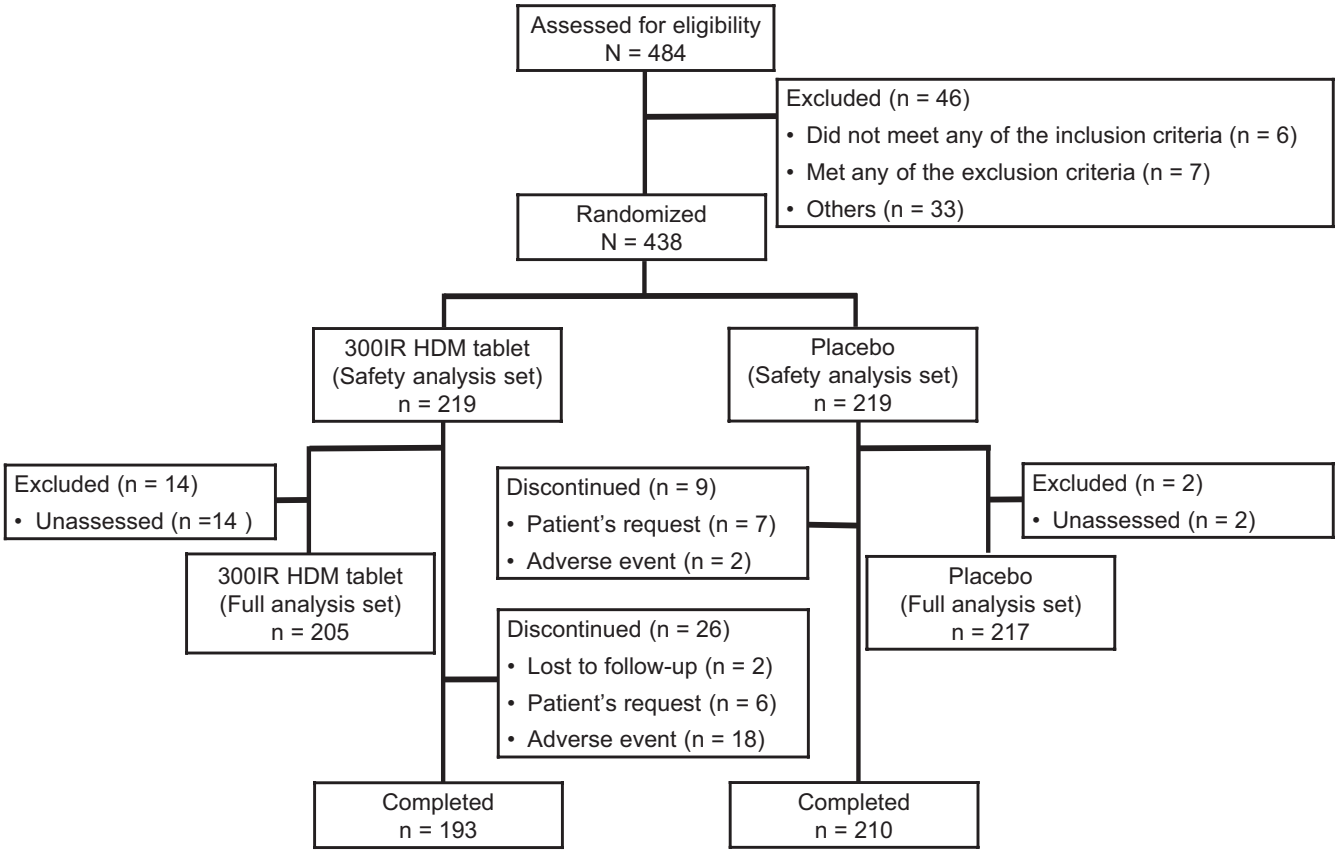

FIGURE 1 Patient disposition. HDM tablet, house dust mite allergen extract tablet; IR, index of reactivity; N/n, number of patients

TABLE 1 Demographics and baseline characteristics (full analysis set)

	HDM tablet N = 205	Placebo N = 217
Age, years		
Mean ± SD	10.3 ± 2.7	10.4 ± 2.7
≥5 to ≤11	130 (63.4)	138 (63.6)
≥12 to ≤16	75 (36.6)	79 (36.4)
Gender		
Male	123 (60.0)	136 (62.7)
Female	82 (40.0)	81 (37.3)
Duration of perennial allergic rhinitis		
<5 y	69 (33.7)	62 (28.6)
≥5 to <10 y	116 (56.6)	137 (63.1)
≥10 y	20 (9.8)	18 (8.3)
Medical history of asthma	26 (12.7)	33 (15.2)
Dermatophagoides pteronyssinus IgE (ImmunoCAP® score)		
0	0	0
1	0	0
2	1 (0.5)	2 (0.9)
3	32 (15.6)	24 (11.1)
4	64 (31.2)	61 (28.1)
5	59 (28.8)	66 (30.4)
6	49 (23.9)	64 (29.5)
Dermatophagoides farinae IgE (ImmunoCAP® score)		
0	0	0
1	0	0
2	0	1 (0.5)
3	28 (13.7)	14 (6.5)
4	60 (29.3)	70 (32.3)
5	59 (28.8)	62 (28.6)
6	58 (28.3)	70 (32.3)
Sensitization with other than house dust mites[a]		
Yes	166 (81.0)	173 (79.7)
No	39 (19.0)	44 (20.3)
Average rhinitis total symptom score		
Mean ± SD	9.69 ± 2.15	9.66 ± 2.19
<8	51 (24.9)	52 (24.0)
≥8 to <10	68 (33.2)	73 (33.6)
≥10	86 (42.0)	92 (42.4)

HDM tablet, house dust mite allergen extract tablet; IgE, immunoglobulin E; N, number of patients; SD, standard deviation.
Data are presented as n (%), unless otherwise stated.
[a]Yes: at least one IgE ImmunoCAP® score is ≥2 (other than *D. pteronyssinus and D. farinae*, the main allergens were Japanese cedar, cat dander, Japanese cypress, cocksfoot, dog dander, and white birch).

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of the 438 randomized patients, 422 (96%; 205 active, 217 placebo) were included in the full analysis set, and 403 (92%; 193 active, 210 placebo) completed the study (Figure 1). Only 8% of patients discontinued, mainly because of an AE.

The demographics and baseline characteristics for the history and severity of allergic airway disease were similar between the active and placebo groups (Table 1). All patients were sensitized to *D. pteronyssinus* and *D. farinae* allergens based on IgE tests and had positive nasal provocation tests. Most patients in both groups had a treatment compliance rate of ≥80% (Table S1).

3.2 | Efficacy

The primary end-point, the AASS (LS mean) during the last 4 weeks of treatment (Weeks 48-52), was significantly lower in the active group compared with placebo ($P = 0.0005$; Figure 2A). The LS mean difference (SE) in AASS between the active and placebo groups was −0.95 (0.27) [relative LS mean difference: −13.1%]. The improvement was observed at the first assessment (Weeks 8-10) and was maintained throughout the 52-week study. The AASS at Weeks 48-52 was significantly lower in the active group compared with placebo in patients aged 5-11 years and 12-16 years (Table S2).

The ARTSS and ACS (LS means) were significantly lower in the active group compared with placebo during the last 4 weeks (Weeks 48-52). There was no significant difference in ARMS (LS mean) between the active and placebo groups. All nasal ISSs were consistently lower in the active group than in the placebo group, with significant differences (Table 2).

The percentage of patients assessed by patients/guardians at Week 52 as "Improved" (sum of "Slight to moderate improvement" and "Marked improvement") was significantly higher in the active group (78.8%) compared with placebo (58.3%, $P < 0.0001$), as was the percentage of patients with general improvement assessed by investigators (67.5% vs 57.4%, $P = 0.0348$; Figure 2B).

3.3 | Immunological responses

The Week 52: baseline ratios of antigen-specific IgE and IgG4 were significantly greater in the active group than with placebo (Figure 3; $P < 0.0001$ for all). *D. pteronyssinus- and D. farinae*-specific IgE antibody levels at Week 52 were higher compared to baseline (1.937- and 1.860-fold, respectively) in the active group, but were relatively unchanged in the placebo group (1.149- and 1.104-fold, respectively). Similarly, IgG4 antibodies to *D. pteronyssinus and D. farinae* at Week 52 were higher compared to baseline (2.741- and 3.362-fold, respectively) in the active group, but remained unchanged (1.086- and 0.987-fold, respectively) in the placebo group.

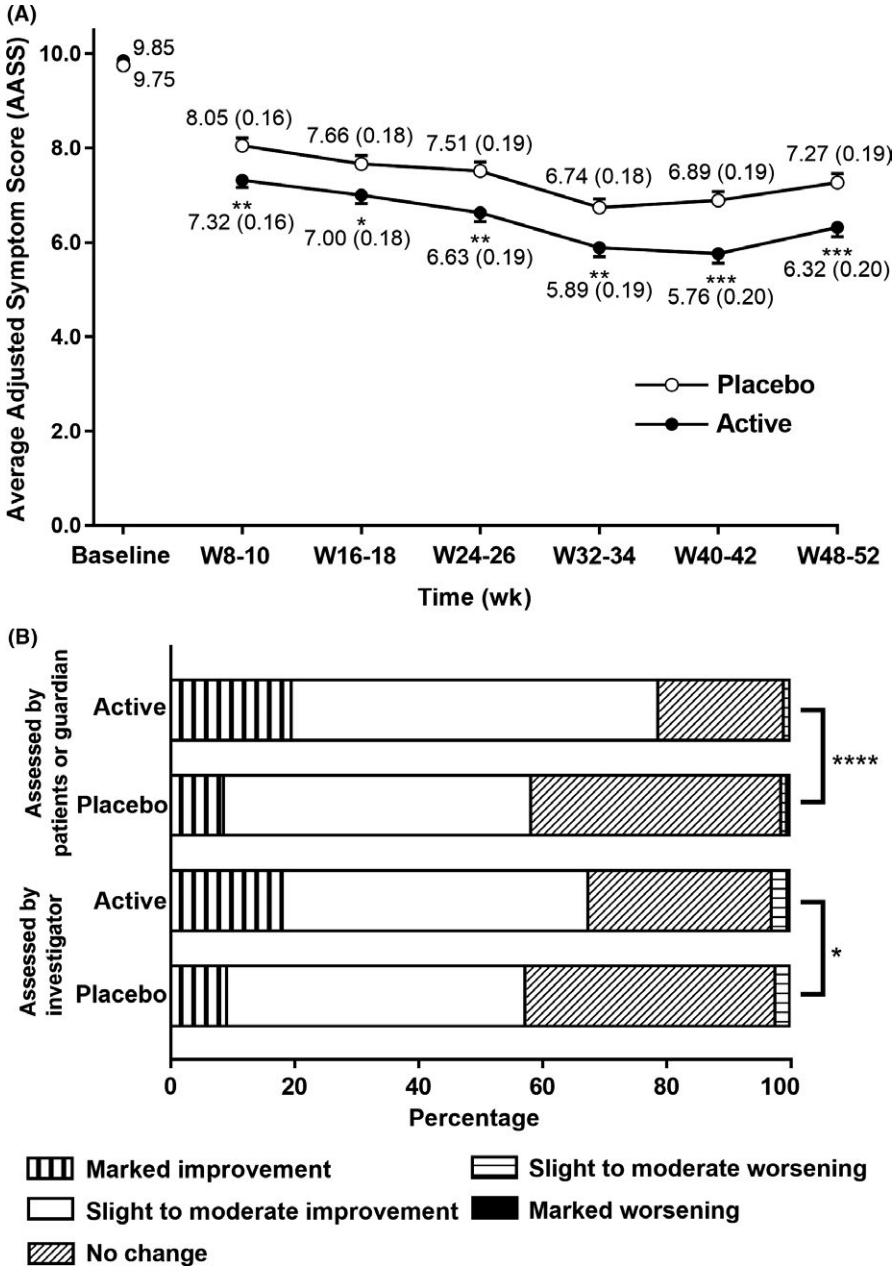

FIGURE 2 A, Time course of the Average Adjusted Symptom Score (AASS) for the 52-week treatment period. The least-squares means and standard errors with the mixed-effects model for repeated measures are shown for the time points at Week 8-10 and later; baseline data are arithmetic mean Average Rhinitis Total Symptom Scores unadjusted for covariates. ***P value < 0.001, **P value < 0.01, *P value < 0.05 compared with placebo. HDM tablet, house dust mite allergen extract tablet. B, Overall assessment of treatment efficacy by patients or guardians and general improvement as assessed by investigators at Week 52. *P value < 0.05, ****P value < 0.0001, percentage of "improved" compared with placebo. HDM tablet, house dust mite allergen extract tablet.

3.4 | Safety and tolerability

Almost all patients reported at least one AE during the study (Table 3). The most common AEs (≥20% of patients) were nasopharyngitis, influenza, pharyngitis (both groups), and oral pruritus (active group only). Treatment-related AEs were reported more frequently in the active group than in the placebo group (67.1% vs 18.3% of patients). The most common treatment-related AEs (≥10% of patients in the active group) were oral pruritus, mouth edema, throat irritation ear pruritus, and mouth swelling.

Most AEs were mild (active: 156 [71.2%], placebo: 162 [74.0%]) or moderate (active: 52 [23.7%], placebo: 44 [20.1%]) in severity. AEs typically occurred between Days 1 and 14, and were more frequent in the active group (72.6%) than in the placebo group (27.4%) during this period.

Eight SAEs were reported by seven patients. In the placebo group, there were two SAEs of upper respiratory tract infection and rheumatic fever (one patient each). In the active group, there were six SAEs in five patients (two patients with gastroenteritis, one patient with pseudocroup [subglottic laryngitis], one patient with both

TABLE 2 Symptom and medication scores at Weeks 48-52 (full analysis set)

Score	HDM tablet N = 205	Placebo N = 217
Average rhinitis total symptom score	6.25 ± 0.19	7.16 ± 0.19
LS mean difference ± SE	−0.91 ± 0.27	—
P value	0.0007	
Relative LS mean difference	−12.7%	—
Average rescue medication score	0.066 ± 0.015	0.072 ± 0.015
LS mean difference ± SE	−0.006 ± 0.021	—
P value	0.7746	
Average combined score	0.81 ± 0.03	0.93 ± 0.03
LS mean difference ± SE	−0.12 ± 0.04	—
P value	0.0010	
Average individual symptom scores		
Sneezing	1.46 ± 0.05	1.71 ± 0.05
LS mean difference ± SE	−0.25 ± 0.08	
P value	0.0014	
Rhinorrhea	1.99 ± 0.06	2.21 ± 0.06
LS mean difference ± SE	−0.22 ± 0.09	
P value	0.0103	
Nasal congestion	1.48 ± 0.06	1.74 ± 0.05
LS mean difference ± SE	−0.26 ± 0.08	
P value	0.0007	
Nasal pruritus	1.32 ± 0.05	1.50 ± 0.05
LS mean difference ± SE	−0.18 ± 0.07	
P value	0.0060	
Itchy eyes	0.85 ± 0.05	0.95 ± 0.05
LS mean difference ± SE	−0.10 ± 0.07	
P value	0.1887	
Watery eyes	0.45 ± 0.04	0.50 ± 0.04
LS mean difference ± SE	−0.05 ± 0.05	
P value	0.3513	

Data are presented as the LS mean ± SE.
Relative LS mean difference: ([Active − Placebo]/Placebo) × 100 (%).
Average Rescue Medication Score: the average of daily Rescue Medication Scores scaled as 0 (no rescue medication), 1 (oral and/or eye drop antihistamine), or 2 (nasal corticosteroid or both corticosteroid and antihistamine).
Average combined score: the average of the daily Combined Scores, where the daily combined score = (RTSS/4 + RMS)/2.
Individual Symptom Score: 0-4 for sneezing, rhinorrhea, nasal congestion, itchy eyes, and watery eyes, and 0-3 for nasal pruritus.
HDM tablet, house dust mite allergen extract tablet; LS mean, least-squares mean; N, number of patients; SE, standard error.

streptococcal infection and viral infection that were resolved, and one patient with fracture that was resolving). Pseudocroup occurred on Day 22, 11 hours after study drug administration; the patient received oral betamethasone, inhaled adrenaline, and inhaled dexamethasone, and recovered on Day 23. The AE was severe, associated with cough and dyspnea, considered to be drug-related by the physician, and led to drug discontinuation. The other patients continued the study with (gastroenteritis [one patient], streptococcal infection, viral infection) or without (gastroenteritis [one patient], fracture) drug interruption. There were no deaths and no anaphylaxis events that required intramuscular adrenaline injection.

4 | DISCUSSION

This definitive, large-scale study has demonstrated the efficacy and safety of sublingual tablets containing standardized allergen extracts of HDM in pediatric patients with perennial AR. In this 52-week, double-blind, randomized, placebo-controlled study, sublingual immunotherapy with HDM allergen extracts was associated with significant and sustained improvement in the symptoms of HDM-induced AR The immunological responses of HDM-specific IgE and IgG4 observed in previous studies were confirmed.[3] The safety profile of the HDM tablets in this pediatric population was consistent with that of adults,[2,3] with no new safety concerns. These results indicate that HDM tablets are effective and well tolerated in pediatric patients with perennial AR, as in adults and adolescents.[2,3]

In this study, sublingual immunotherapy with HDM tablets was associated with significant and sustained (up to 1 year) improvement in symptoms of HDM-induced AR, compared with placebo. AASS was statistically significantly lower in the active group compared with placebo. Improvements in AASS were observed in the first evaluation period (Weeks 8-10) and maintained thereafter, suggesting that the onset of action of HDM tablets occurs within the first 10 weeks of treatment. In addition, the significant improvement in AASS was observed in

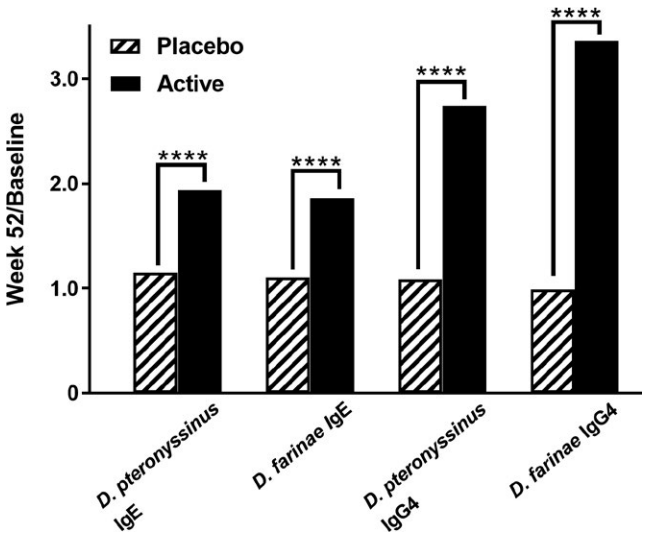

FIGURE 3 House dust mite-specific serum immunoglobulins. Geometric means of the Week 52/baseline ratio are shown. ****P value < 0.0001 compared with placebo. IgE, immunoglobulin E; IgG4, immunoglobulin G4.

TABLE 3 Incidence of adverse events (safety analysis set)

Adverse events	HDM tablet N = 219	Placebo N = 219
Patients with any AEs	212 (96.8)	207 (94.5)
Serious AEs	5 (2.3)	2 (0.9)
AEs leading to discontinuation	18 (8.2)	2 (0.9)
Patients with any treatment-related AEs	147 (67.1)	40 (18.3)
Serious treatment-related AEs	1 (0.5)	0
Treatment-related AEs leading to discontinuation	16 (7.3)	0
AEs with incidence ≥5% in the active group[a]		
Infections and infestations	172 (78.5)	189 (86.3)
Nasopharyngitis	93 (42.5)	116 (53.0)
Influenza	57 (26.0)	68 (31.1)
Pharyngitis	51 (23.3)	54 (24.7)
Acute sinusitis	30 (13.7)	30 (13.7)
Gastroenteritis	23 (10.5)	15 (6.8)
Bronchitis	13 (5.9)	20 (9.1)
Upper respiratory tract infection	11 (5.0)	16 (7.3)
Immune system disorders	11 (5.0)	13 (5.9)
Seasonal allergy	11 (5.0)	12 (5.5)
Nervous system disorders	15 (6.8)	13 (5.9)
Ear and labyrinth disorders	32 (14.6)	4 (1.8)
Ear pruritus	27 (12.3)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	96 (43.8)	31 (14.2)
Throat irritation	33 (15.1)	4 (1.8)
Oropharyngeal discomfort	19 (8.7)	3 (1.4)
Epistaxis	15 (6.8)	9 (4.1)
Cough	13 (5.9)	4 (1.8)
Oropharyngeal pain	12 (5.5)	2 (0.9)
Gastrointestinal disorders	138 (63.0)	56 (25.6)
Oral pruritus	47 (21.5)	4 (1.8)
Mouth edema	36 (16.4)	0
Mouth swelling	22 (10.0)	1 (0.5)
Abdominal pain	19 (8.7)	5 (2.3)
Stomatitis	15 (6.8)	20 (9.1)
Vomiting	12 (5.5)	3 (1.4)
Skin and subcutaneous tissue disorders	36 (16.4)	45 (20.5)
Eczema	11 (5.0)	17 (7.8)
General disorders and administration site conditions	20 (9.1)	10 (4.6)
Injury, poisoning, and procedural complications	38 (17.4)	33 (15.1)

AE, adverse event; HDM tablet, house dust mite allergen extract tablet; N, number of patients.
Data are presented as n (%) of patients.
[a]Listed by System Organ Class and Preferred Term, Medical Dictionary for Regulatory Activities (MedDRA), version 18.0.

both younger (aged 5-11 years) and older (aged 12-16 years) patients. Similarly, ARTSS, ACS, and all nasal ISSs were also significantly lower with the HDM tablets compared with placebo, consistent with previous studies.[2,3] Although there was a tendency for ocular symptoms and ARMS to be improved with active treatment, there were no statistically significant between-group differences, most likely because ocular symptoms were mild at both baseline (data not shown) and at Weeks 48-52, and because very few patients in either group were treated with rescue medication. The relatively low level of ocular involvement at baseline is unsurprising given that nasal symptoms are predominant in HDM AR (as opposed to allergy to outdoor allergens, where ocular symptoms are more common).[9] Finally, more patients/guardians and investigators considered the overall assessment as having improved with HDM tablets compared with placebo at Week 52, as in adults and adolescents.[3]

The immunological response of HDM-specific IgE and IgG4 to HDM tablets previously observed in adults and adolescents[3] was confirmed in pediatric patients. In Japanese adults and adolescents with AR who received HDM tablets, the levels of *D. pteronyssinus- and D. farinae*-specific antibodies at Week 52 were increased 1.8- and 1.9-fold (IgE) and 2.6- and 3.7-fold (IgG4) compared with baseline.[3] A European study also reported increased IgG4 (although not IgE) in adults treated with HDM tablets at a 300IR dose.[2] However, the relatively immature immune system in children, especially young children, should be considered when comparing immune responses to those of adults.

The safety profile of HDM tablets in Japanese pediatric patients was consistent with that of adults and adolescents.[2,3] Although no new safety concerns were observed, the incidence rates of AEs in both treatment groups (96.8% in the active group and 94.5% in the placebo group) were higher than previously reported in adults and adolescents.[2,3] This may be related to the long study duration and a higher incidence of infectious disease in pediatric patients compared with adults. Although almost all patients reported an AE during the study, most were mild to moderate and typically occurred during the first 2 weeks of treatment. Further, the incidence of treatment-related AEs in our pediatric population is similar to that reported in Japanese adult and adolescent populations.[3] Importantly, and similar to previous studies, there were no events of anaphylaxis that required adrenaline injection.[2,3] However, as expected with any sublingual immunotherapy,[10,11] severe allergic reactions affecting upper and lower airways, skin, conjunctiva, and multiple organ systems individually or in combination may be expected. Therefore, patients and their guardians should be instructed on how to recognize the early signs and symptoms of these reactions.

The strengths of this study include its randomized, placebo-controlled design, duration (52 weeks), large number of efficacy and safety outcomes, and adjustment for baseline values in the statistical analysis. However, the study did not evaluate whether the treatment effects last beyond 52 weeks of treatment, did not use objective measures such as peak nasal inspiratory flow or the nasal provocation test (which was used only at baseline), and did not measure the levels of HDM allergens in households. Nevertheless,

this immunotherapy should be an important part of AR therapy because nasal congestion, which is difficult to treat, was significantly improved.

In conclusion, sublingual immunotherapy with HDM tablets at a dose of 300IR was associated with significant and sustained improvement in symptoms of HDM-induced AR and had an acceptable safety and tolerability profile that was consistent with adults and adolescents. These results suggest that HDM tablets administered at 300IR once daily are an effective and well-tolerated option for pediatric patients with perennial AR

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CONFLICT OF INTERESTS

YO has received grant and personal fees from Torii, Shionogi, Kyowa Hakko Kirin, Kyorin, Taiho, and Mitsubishi Tanabe; grants from Yamada Bee Farm and Yakult; and personal fees from Stallergenes Greer, GSK, MSD, Sanofi, Thermo Fisher Scientific, Taisyo Toyama, Nippon Zoki, and Otsuka. SF has received grant and personal fees from Shionogi. MO has received personal fees from Torii, Kyorin, Mitsubishi Tanabe, and Shionogi. KM has received grants and personal fees from Torii, Shionogi, Taiho, Sanofi, Merk Serono, Eisai, and Mitsubishi Tanabe, a grant from Tsumura, and personal fees from GSK, MSD, Kyorin, Meiji Seika, Medical Review, Taisho Toyama, and Nihonshinyaku. HH and SK are employees of, and own stock in, Shionogi.

AUTHOR CONTRIBUTION

All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript. YO, SF, MO, HH, SK, and KM were involved in the study design. HH and SK were involved in the data collection. HH conducted the statistical analyses. All authors were involved in the interpretation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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