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Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet in Japanese children

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Abstract

Background: The SQ house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet (TO-203, Torii, Japan/ALK, Denmark) treatment has been effective against respiratory allergic diseases in patients aged ≥12 years during European, Japanese, and North American trials. This trial was conducted to investigate the efficacy and safety of this treatment in Japanese children (5-17 years) with moderate-to-severe HDM allergic rhinitis (AR).

Methods: In this randomized, double-blind, placebo-controlled trial, 458 Japanese children were randomly assigned to a daily SQ HDM SLIT-tablet [10 000 Japanese Allergy Unit (JAU), equivalent to 6 SQ-HDM in Europe and the US] or placebo (1:1) treatment for 1 year. Inclusion required an AR symptom score of ≥7 on at least 7 days during a 14-day run-in period while symptomatic treatment was withdrawn. The primary endpoint was the total combined rhinitis score (TCRS) comprising AR symptom and medication scores during the last 8 weeks of the treatment period.

Results: The analysis of primary endpoint demonstrated statistically significant absolute reduction in TCRS of 1.22 with a relative difference of 23% (95% confidence interval, 14% to 31%) in the 10 000 JAU compared with placebo. Predefined stratified analyses revealed the same degree of efficacy of 1.11 (P = 0.002), 21% (8% to 32%) and 1.36 (P = 0.001), 26% (11% to 38%), respectively, in pediatric (5-11 years) and adolescent subjects (12-17 years). The treatment was well tolerated by both pediatric and adolescent subjects.

Conclusion: This trial, for the first time, demonstrated the efficacy and safety of the HDM SLIT-tablet in pediatric patients with moderate-to-severe HDM AR (JapicCTI-152953).

KEYWORDS
adolescent, allergy immunotherapy, house dust mite, pediatric, sublingual immunotherapy

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AIT, allergy immunotherapy; AR, allergic rhinitis; CI, confidence interval; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*; e-diary, electronic diary; FAS, full analysis set; GINA, global initiative for asthma; HDM, house dust mite; ITT, intention-to-treat; JAU, Japanese Allergy Unit; JRQLQ, Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire; LME, linear mixed effect; MMRM, mixed-model repeated measures; PPS, per-protocol analysis set; QoL, quality of life; SAE, serious adverse event; SD, standard deviation; SLIT, sublingual immunotherapy; TCRS, total combined rhinitis score.

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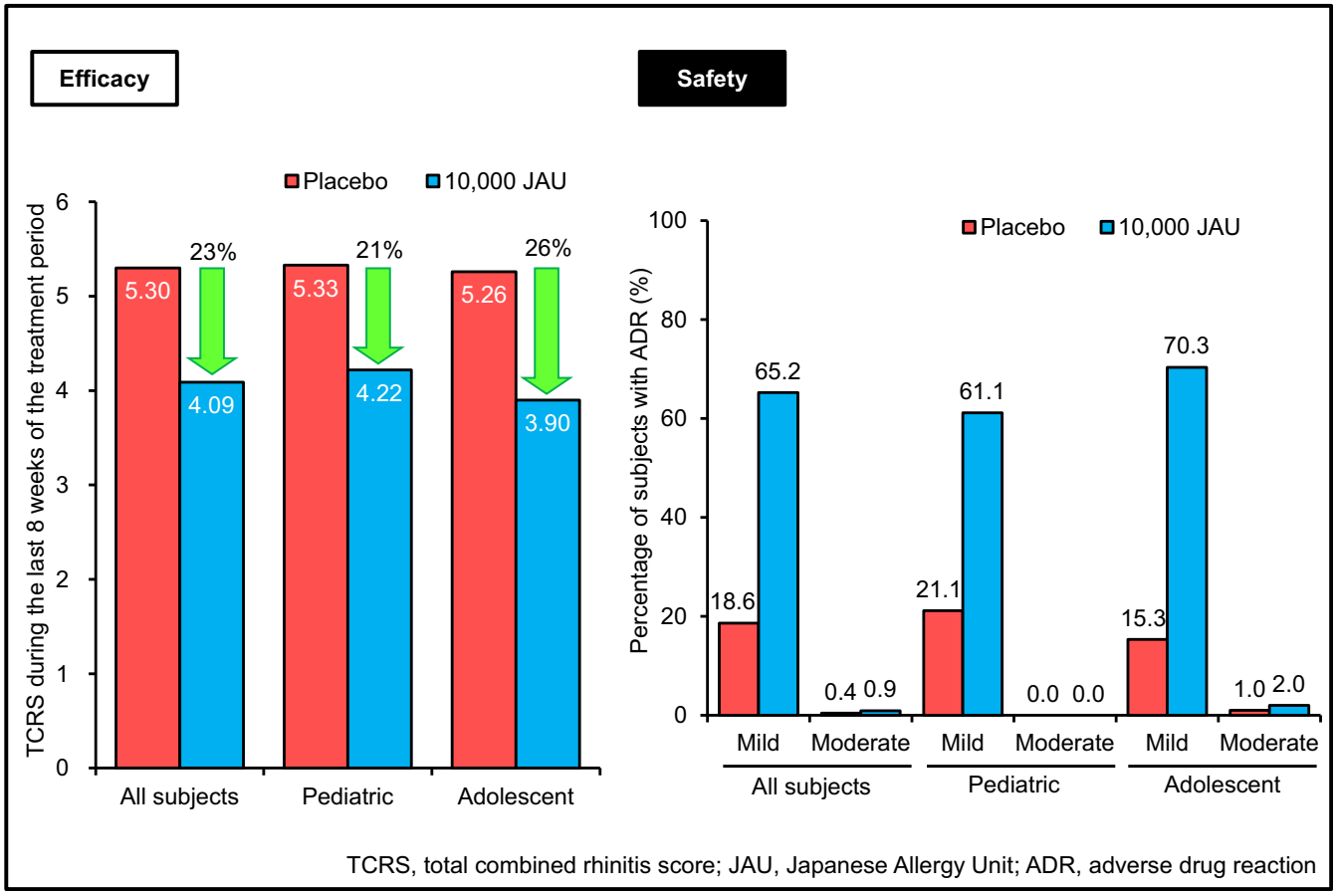

GRAPHICAL ABSTRACT

This randomized, double-blind, placebo-controlled phase III clinical trial demonstrated the efficacy and favorable safety profile of the SQ HDM SLIT-tablet in Japanese pediatric and adolescent patients with moderate-to-severe HDM-induced AR. The 10 000 JAU group showed statistically significant improvement compared with placebo group in primary endpoint, TCRS during the last 8 weeks of the treatment period. No relevant difference in the efficacy and safety profile was observed between pediatric and adolescent subjects. HDM, house dust mite; SLIT, sublingual immunotherapy; AR, allergic rhinitis; JAU, Japanese allergy unit; TCRS, total combined rhinitis score.

1 | INTRODUCTION

Allergy immunotherapy (AIT) has the potential benefit of being able to modulate immunologic mechanisms in patients with allergic diseases.[1] Besides providing symptom relief, AIT contributes to improvements in the quality of life (QoL) of patients with allergies. With 3 to 5 years of treatment duration, these effects have been shown to be lasting to post-treatment.[2-6]

Dermatophagoides pteronyssinus (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*), two species of house dust mites (HDMs), are some of the most important allergens in pediatric and adolescent patients.[7,8] In Japan, the prevalence of perennial allergic rhinitis (AR) is 4% in children below 5 years, 22.5% in children aged 5 to 9 years, and 36.6% in children aged 10 to 19 years.[9] These are values that are higher than those for seasonal allergies. Among inhalant allergens, HDM sensitization was found to be the most important risk factor for asthma development in children.[10-14] AIT is currently the only treatment option with the potential to prevent asthma development in pediatric and adolescent patients with allergic rhinitis.[4,5,15,16] Thus, it is important that allergic diseases are treated at an early age by AIT.

The SQ HDM sublingual immunotherapy (SLIT)-tablet (TO-203, Torii, Japan/ALK, Denmark) is a fast-dissolving pharmaceutical formulation manufactured and provided by ALK. Based on confirmatory results during the clinical trials,[17-22] the SQ HDM SLIT-tablet has been approved in Europe for the treatment of HDM allergic asthma in patients aged 18 to 65 years and for HDM AR in patients 12 to 65 years. It has also been approved in Japan for HDM AR in patients aged 12 years or older and in the United States and Canada for patients aged 18 to 65 years. The present trial was initiated to investigate the efficacy and safety of the SQ HDM SLIT-tablet in Japanese pediatric and adolescent patients with moderate-to-severe HDM AR. The adolescent population included in this trial was different from the ones included in the previous trial.[21]

2 | METHODS

2.1 | Trial design

This randomized, double-blind, placebo-controlled trial was conducted at 66 sites within Japan from July 2015 to November 2016 (JapicCTI number 152953). A total of 458 subjects were randomized (1:1) to either the Japanese marketed dose of 10 000 Japanese Allergy Unit (JAU) or placebo. The randomization was performed in mixture blocks of two and four via an interactive Web response system programmed by Bell Medical Solutions, Inc. (Tokyo, Japan). Subjects initiated daily SQ HDM SLIT-tablet treatment at a dose of 3300 JAU or placebo for a week. From week 2 and onward, the subjects received 10 000 JAU or placebo throughout the remainder of the trial, which was approximately 51 weeks. The sponsors, subjects, investigators, and trial personnel were blinded to the treatment until database lock. The trial design is shown in this article's Online Repository (Figure E1).

The trial complied with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the Institutional Review Board of each clinical site. Written informed consent was obtained from the subjects and their legal representatives.

2.2 | Trial population

Japanese pediatric and adolescent subjects aged 5 to 17 years with moderate-to-severe HDM AR were screened from July to October 2015. Subjects were stratified by age to ensure that at least 50% of randomized subjects were pediatrics. Main inclusion criteria included a medication history for HDM AR of at least 1 year; a positive nasal provocation test to house dust; a positive specific serum IgE level (≥3.5 kU/L) against *D. pteronyssinus*, *D. farinae*, or both; and an AR symptom score of 7 or more on at least 7 days of the 14-day run-in period as the definition of "moderate-to-severe" while symptomatic treatment was withdrawn. Main exclusion criteria were asthma requiring treatment with inhaled corticosteroid; specific serum IgE levels of 50 kU/L or above in any one of the following allergens: cedar, cypress, alder, birch species, cocksfoot, ragweed, mugwort, Japanese hop, cockroach, *Candida* species, *Aspergillus* species, *Alternaria* species, dog dander, or cat dander; or a clinically relevant history of symptomatic AR caused by the following allergens: cocksfoot, ragweed, mugwort, Japanese hop, cockroach, *Candida* species, *Aspergillus* species, *Alternaria* species, dog dander, or cat dander.

Details on the main selection criteria are available in the Methods section in this article's Online Repository.

2.3 | Intervention medication

The SQ HDM SLIT-tablet (TO-203, Torii, Japan; manufactured by ALK, Denmark) is a fast-dissolving freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *D. pteronyssinus* and *D. farinae*, with a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2.[23,24] The common unit for HDM AIT products in Japan is JAU, and 22.2 to 66.7 μg/mL of Der 1 (Der f 1 and Der p 1 combined) was defined as 100 000 JAU/mL by the Japanese Society of Allergology Task Force in 2014.[25] A nominal strength of 10 000 JAU has the same potency as 6 SQ-HDM (the unit used in Europe and the US). The placebo tablets were similar to the active intervention medication with regard to appearance, smell, and taste.

For safety purposes, the first administration was performed at the clinical site, followed by a 30-min observation under medical supervision. Subsequent administrations at home were advised to be under adult supervision for the pediatric subjects (5 to 11 years). Similar to our previous trial,[21] allergy pharmacotherapy, in terms of antihistamine tablets and eyedrops or nasal steroids, was provided to the subjects as rescue medications. Pediatric subjects who were unable to swallow an antihistamine tablet were given dry sirup preparations. Allergy pharmacotherapy was only to be used in case of intolerable symptoms.

2.4 | Assessments

Symptom and medication scores were evaluated using methods similar to those in our previous trial in compliance with the European Medicines Agency guidelines.[26] The primary endpoint was the total combined rhinitis score (TCRS; ie, the sum of rhinitis symptom and medication scores; total range, 0-24). Details on the scoring scales have been published previously.[21] Adolescents and legal representatives of pediatric subjects entered the scores into the electronic diary (e-diary) every evening during the run-in period, 2 weeks after each visit at weeks 4, 12, 20, 28, and 36, and during the primary evaluation period (the last 8 weeks of the 52-week treatment period; Figure E1). The primary evaluation period was from August to November. When the representatives were not able to evaluate the daytime symptoms, an easy memorandum was provided to the pediatric subjects (5 to 11 years) so that they themselves could record their daytime symptoms. The representatives compared their evaluation with that in the memorandum to confirm whether a large discrepancy existed. The final reported data were determined by the representatives. Adolescents and legal representatives of pediatric subjects completed the Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire (JRQLQ)[9] during randomization and at weeks 4, 28, 44, and 52 at the clinical sites. Global evaluation, which was composed of five grades from much better to much worse, was performed by adolescents, legal representatives of pediatric subjects, and physicians at the end of the treatment. Serum was collected at randomization and at weeks 4, 12, and 52 for the analysis of HDM-specific IgE and IgG_4 levels. The safety profile was assessed by gathering information regarding treatment-emergent adverse events (AEs) and adverse drug reactions (ADRs) defined as AEs assessed as related to the investigational medicinal product.

2.5 | Statistics

Sample size calculations were based on the results of our previous trial.[21] There was a power of approximately 88% to detect a

TABLE 1 Baseline characteristics and demography

Treatment group	Placebo N = 231	10 000 JAU N = 227	5-11 years		12-17 years	
			Placebo N = 133	10 000 JAU N = 126	Placebo N = 98	10 000 JAU N = 101
Male, no (%)	154 (66.7)	150 (66.1)	86 (64.7)	83 (65.9)	68 (69.4)	67 (66.3)
Monosensitized, no (%)	74 (32.0)	51 (22.5)	54 (40.6)	29 (23.0)	20 (20.4)	22 (21.8)
Asthma, no (%)	6 (2.6)	10 (4.4)	4 (3.0)	6 (4.8)	2 (2.0)	4 (4.0)
Age (year)						
Mean ± SD	10.7 ± 3.1	10.8 ± 2.9	8.5 ± 1.9	8.6 ± 1.7	13.8 ± 1.5	13.5 ± 1.5
Median (Min-Max)	11.0 (5-17)	11.0 (5-17)	9.0 (5-11)	9.0 (5-11)	13.5 (12-17)	13.0 (12-17)
Years with HDM AR						
Mean ± SD	5.2 ± 3.5	5.2 ± 3.0	3.7 ± 2.4	4.1 ± 2.1	7.2 ± 3.7	6.6 ± 3.3
Median(Min-Max)	5.0 (0-16)	5.0 (1-14)	3.0 (0-10)	4.0 (1-9)	7.0 (1-16)	6.0 (1-14)
Onset (year)						
Mean ± SD	5.5 ± 3.1	5.6 ± 3.1	4.8 ± 2.5	4.5 ± 2.3	6.5 ± 3.6	6.9 ± 3.4
Median (Min-Max)	5.0 (0-13)	5.0 (0-15)	5.0 (0-11)	4.0 (0-10)	6.5 (0-13)	7.0 (0-15)
Specific IgE (kU/L), *D. farinae*, no. (%)						
<17.5	29 (12.6)	21 (9.3)	19 (14.3)	8 (6.3)	10 (10.2)	13 (12.9)
≥17.5 to <50	71 (30.7)	76 (33.5)	30 (22.6)	39 (31.0)	41 (41.8)	37 (36.6)
≥50 to <100	76 (32.9)	60 (26.4)	49 (36.8)	36 (28.6)	27 (27.6)	24 (23.8)
≥100	55 (23.8)	70 (30.8)	35 (26.3)	43 (34.1)	20 (20.4)	27 (26.7)
Specific IgE (kU/L), *D. pteronyssinus*, no. (%)						
<17.5	42 (18.2)	30 (13.2)	26 (19.5)	12 (9.5)	16 (16.3)	18 (17.8)
≥17.5 to <50	65 (28.1)	78 (34.4)	30 (22.6)	44 (34.9)	35 (35.7)	34 (33.7)
≥50 to <100	62 (26.8)	52 (22.9)	37 (27.8)	28 (22.2)	25 (25.5)	24 (23.8)
≥100	62 (26.8)	67 (29.5)	40 (30.1)	42 (33.3)	22 (22.4)	25 (24.8)
AR symptom score						
Mean ± SD	8.59 ± 1.38	8.55 ± 1.40	8.45 ± 1.25	8.56 ± 1.45	8.78 ± 1.52	8.53 ± 1.34
Median (Min-Max)	8.43 (6.3-12.0)	8.21 (5.9-12.0)	8.36 (6.3-12.0)	8.21 (5.9-12.0)	8.54 (6.4-12.0)	8.21 (6.4-12.0)

JAU, Japanese Allergy Unit; SD, standard deviation; Min, minimum; Max, maximum; HDM, house dust mite; AR, allergic rhinitis; kU/L, kilo-units per liter; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*.

difference between the 10 000 JAU and placebo groups, each having 200 subjects, including an estimated discontinuation rate of 10%. The primary analysis utilized the linear mixed-effect (LME) model using the AR symptom score at baseline and the treatment group as fixed effects and clinical site as a random effect. A linear model, which did not include the clinical site as a random effect, was performed for the age subgroup analysis because of differences in the number of clinical sites. The primary analysis set was the full analysis set (FAS), which was defined as all subjects who entered at least 80% of the information regarding symptom scores and medication use into the e-diary during the primary evaluation period. Additional analysis sets for the primary endpoint included the per-protocol analysis set (PPS), with included subjects who had no significant protocol deviations. Subjects who recorded symptom scores and medication use at least once during the course of the trial were classified under the intention-to-treat (ITT) population and were analyzed using mixed-model repeated measures (MMRM). The method for analyzing the AR symptom score, the prespecified key secondary endpoint, was the same as for the primary endpoint. Percent days of AR symptom-free and -severe days except week 44-52 were performed by post hoc analysis. Details on sample size calculations and statistical analyses are available in the Methods section and Table E1 in this article's Online Repository.

3 | RESULTS

3.1 | Population

Subject disposition is shown in this article's Online Repository (Figure E2). Informed consent was obtained from 735 patients, of whom 458 were randomized to either placebo or 10 000 JAU treatment group. The number of subjects who discontinued due to AEs as assessed by the physicians did not differ between the two groups, whereas one and six patients from the placebo and 10 000 JAU groups, respectively, withdrew their consent due to AEs. In total, 217 subjects (94%) in the placebo group and 209 subjects (92%) in the 10 000 JAU group completed the trial. All subjects had entered at least 80% of the e-diary during the last 8 weeks of the treatment period. One subject from the placebo group, who discontinued the

TABLE 2 Analyses of the symptom, medication, and combined scores during the primary evaluation period (weeks 44-52)

Analysis set		Treatment group	N	Adjusted mean	Absolute difference from placebo (95% CI)	*P* value	Relative difference to placebo (95% CI)
Primary endpoint: TCRS							
FAS	LME	All subjects					
		Placebo	218	5.30	–	–	–
		10 000 JAU	209	4.09	1.22 (0.69 to 1.74)	<0.001	23% (14% to 31%)
	Linear model	5-11 years					
		Placebo	129	5.33	–	–	–
		10 000 JAU	118	4.22	1.11 (0.41 to 1.80)	0.002	21% (8% to 32%)
		12-17 years					
		Placebo	89	5.26	–	–	–
		10 000 JAU	91	3.90	1.36 (0.54 to 2.19)	0.001	26% (11% to 38%)
ITT (MMRM)		Placebo	231	5.37	–	–	–
		10 000 JAU	221	4.07	1.30 (0.78 to 1.82)	<0.001	24% (15% to 32%)
PPS (LME)		Placebo	214	5.27	–	–	–
		10 000 JAU	202	4.12	1.16 (0.62 to 1.69)	<0.001	22% (12% to 30%)
Key secondary endpoint: AR symptom score							
FAS	LME	All subjects					
		Placebo	218	5.10	–	–	–
		10 000 JAU	209	3.95	1.15 (0.66 to 1.64)	<0.001	23% (14% to 31%)
	Linear model	5-11 years					
		Placebo	129	5.13	–	–	–
		10 000 JAU	118	4.05	1.08 (0.43 to 1.73)	0.001	21% (9% to 32%)
		12-17 years					
		Placebo	89	5.06	–	–	–
		10 000 JAU	91	3.80	1.26 (0.50 to 2.02)	0.001	25% (11% to 37%)
Other secondary endpoint (FAS) (LME)							
AR medication score		Placebo	218	0.06	–	–	–
		10 000 JAU	209	0.03	0.03 (0.00 to 0.06)	0.028	56% (8% to 83%)
Combined conjunctivitis score		Placebo	218	0.91	–	–	–
		10 000 JAU	209	0.56	0.34 (0.17 to 0.52)	<0.001	38% (20% to 52%)
Conjunctivitis symptom score		Placebo	218	0.81	–	–	–
		10 000 JAU	209	0.51	0.29 (0.13 to 0.46)	<0.001	36% (18% to 51%)
Conjunctivitis medication score		Placebo	218	0.02	–	–	–
		10 000 JAU	209	0.01	0.01 (0.00 to 0.03)	0.039	56% (4% to 83%)

CI, confidence interval; TCRS, total combined rhinitis score; LME, linear mixed effect; FAS, full analysis set; ITT, intention-to-treat; MMRM, mixed-model repeated measures; PPS, per-protocol analysis set; JAU, Japanese Allergy Unit; AR, allergic rhinitis.
Adjusted means are mean of scores during week 44 to 52.

trial prematurely during the last 8 weeks of the treatment period, was included in the FAS because the subject discontinued after entering more than 80% of the e-diary. The FAS of the placebo group therefore included 218 subjects.

Table 1 shows the subject baseline characteristics and demography. A comparison of the placebo and 10 000 JAU groups by age revealed a major difference in the rate of HDM monosensitization with 32.0% in the placebo group and 22.5% in the 10 000 JAU group. This difference was evident in the pediatric subgroup alone, in which 40.6% of the subjects were monosensitized in the placebo group compared with 23.0% in the active group. The other baseline characteristics were found to be fairly similar between groups (details on each symptom score at baseline for both population are available in Table E2 in this article's Online Repository).

3.2 | Efficacy

The primary and key secondary endpoints were the total combined rhinitis score (TCRS) and AR symptom score during the last 8 weeks of the treatment period (primary evaluation period). Moreover,

TABLE 3 Symptom relief evaluation during the primary evaluation period (weeks 44-52), and QoL and Global Evaluation at week 52 (FAS)

			t test			Logistic regression		
				Against placebo			Against placebo	
Symptom	Treatment group	N	Days mean (SD)	Absolute difference (95% CI)	*P* value	Probability (%)[a]	Odds ratio (95% CI)	*P* value
Symptom-free days								
AR	Placebo	218	3.0 (8.8)	–	–	20.9	–	–
	10 000 JAU	209	5.7 (12.8)	2.7 (0.6 to 4.7)	0.013	35.6	2.09 (1.36 to 3.23)	0.001
Conjunctivitis	Placebo	218	26.2 (22.9)	–	–	76.4	–	–
	10 000 JAU	209	30.9 (22.6)	4.8 (0.4 to 9.1)	0.031	86.7	2.02 (1.23 to 3.32)	0.006
Symptom-severe days								
AR	Placebo	218	10.9 (16.5)	–	–	24.6	–	–
	10 000 JAU	209	7.4 (13.0)	3.5 (0.7 to 6.3)	0.015	37.5	1.84 (1.21 to 2.80)	0.004
Conjunctivitis	Placebo	218	2.3 (6.4)	–	–	67.5	–	–
	10 000 JAU	209	1.5 (5.9)	0.9 (–0.3 to 2.0)	0.155	80.4	1.97 (1.26 to 3.08)	0.003
QoL[b]			0: Fine	1	2	3	4: Crying	*P* value[c]
JRQLQ general state	Placebo	217[d]	17 (7.8)	82 (37.8)	72 (33.2)	44 (20.3)	2 (0.9)	–
	10 000 JAU	209	29 (13.9)	94 (45.0)	63 (30.1)	19 (9.1)	4 (1.9)	0.001
Global evaluation[b]			Much better	Better	The same	Worse	Much worse	*P* value[c]
Physician	Placebo	217[d]	58 (26.7)	65 (30.0)	70 (32.3)	18 (8.3)	6 (2.8)	–
	10 000 JAU	209	92 (44.0)	76 (36.4)	36 (17.2)	4 (1.9)	1 (0.5)	<0.001
Subject	Placebo	217[d]	46 (21.2)	87 (40.1)	73 (33.6)	10 (4.6)	1 (0.5)	–
	10 000 JAU	209	72 (34.4)	100 (47.8)	32 (15.3)	4 (1.9)	1 (0.5)	<0.001

SD, standard deviation; CI, confidence interval; AR, allergic rhinitis; JAU, Japanese Allergy Unit; QoL, quality of life; JRQLQ, Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire.

[a]Subjects with at least one "symptom-free day," or no "symptom-severe days" during the primary evaluation period.

[b]N (%).

[c]Wilcoxon rank-sum test.

[d]JRQLQ and Global Evaluations of one subject were not recorded at the end of treatment period due to a SAE, despite completing more than 80% of the e-diary during the primary evaluation period.

stratified analyses by age, pediatrics (5 to 11 years) and adolescents (12 to 17 years), for the primary and key secondary endpoints were performed (Table 2). The 10 000 JAU group showed an absolute reduction in TCRS compared to placebo group of 1.22 ($P < 0.001$, 95% confidence interval (CI): 0.69 to 1.74) for the FAS analysis. This is a 23% improvement compared to placebo (95%CI: 14 to 31%). For the ITT and PPS, the absolute reductions were ≥1, a relative improvements were ≥20%, and a 95% CI upper limit of ≥10%. Similar results were obtained when analyzed by age. AR symptom scores during the primary evaluation period also showed analytical results that were similar to those for TCRS both in all subjects and by age. The AR symptom score during the primary evaluation period was reduced by 49.0% from baseline in the 10 000 JAU group while the placebo group showed 36.4% reduction (Table E3). All other symptom, medication, and combined scores significantly improved against placebo (details on the results for each symptom score during the primary evaluation period are available in the Results section and Table E4 in this article's Online Repository).

Table 3 presents the results of the clinical relevance evaluation. Symptom-free and -severe days for both AR and conjunctivitis, including their probabilities, during the primary evaluation period significantly improved in the 10 000 JAU group compared with the placebo group, except for conjunctivitis symptom-severe days, which showed numerical improvement. The general state of the JRQLQ and the global evaluation by subjects and physicians reached all significantly improved in the 10 000 JAU group compared with the placebo group at week 52.

The differences between the placebo and 10 000 JAU groups in adjusted mean TCRS and AR symptom scores were statistically significant after 4 weeks of treatment, and the difference increased as the treatment progressed (Figure 1A,B). The difference between the placebo and 10 000 JAU groups in adjusted mean AR medication scores was statistically significant after 12 weeks of treatment except 36 to 38 weeks (Figure 1C). The percentages of AR symptom-severe days between the two groups were numerically different throughout the trial. Although no difference was identified between the two groups in the percentage of AR symptom-free days during the initial stage of treatment, a difference emerged in the latter half of the treatment period and was statistically significant during primary evaluation period (Figure 1D).

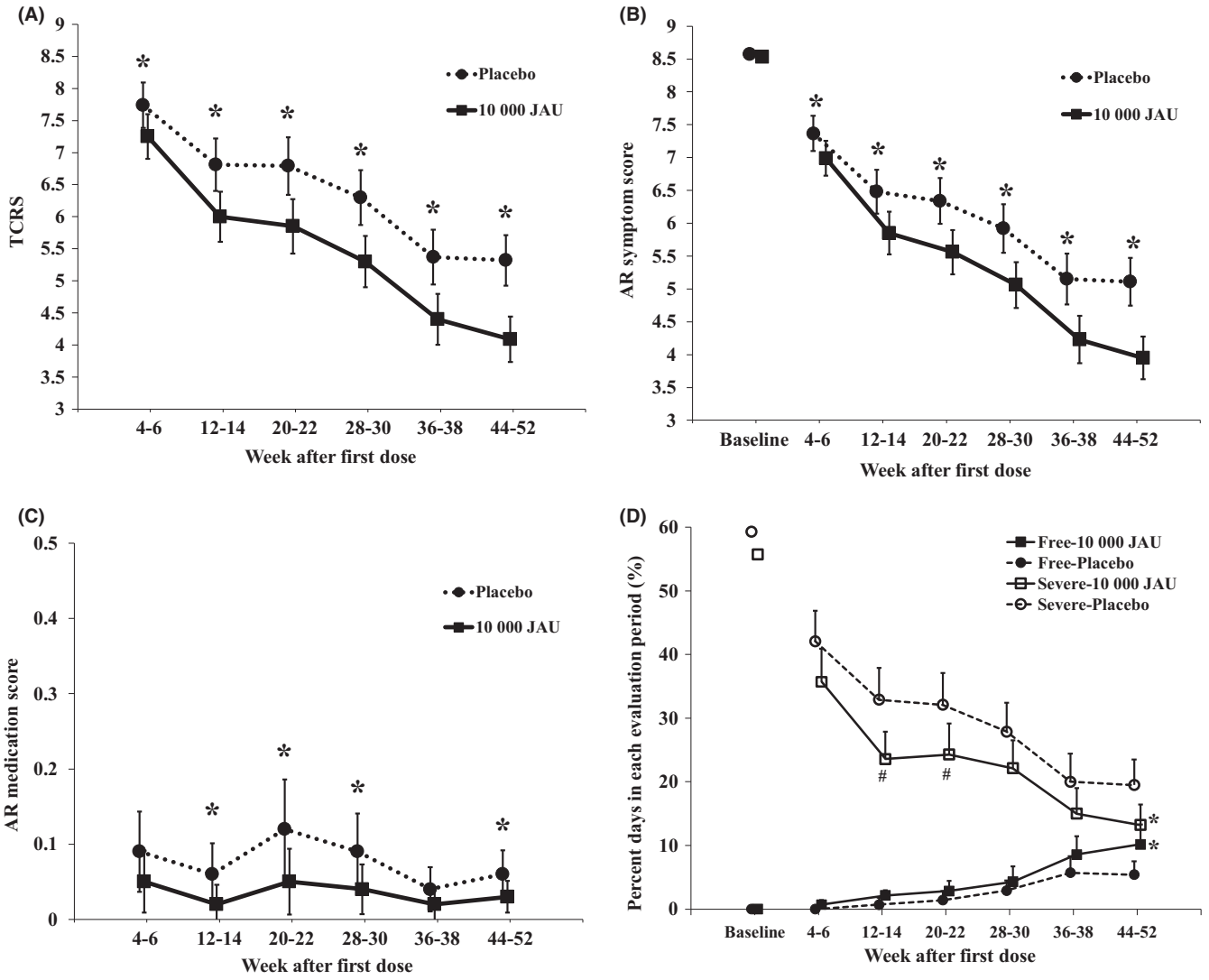

FIGURE 1 Adjusted means with 95% CIs of TCRSs (A), AR symptom scores (B), AR medication scores (C), and percentage of AR symptom-free and -severe days (D) throughout the 52-week treatment period (primary evaluation period: weeks 44-52) (ITT). The isolated symbols at baseline in the (B) and (D) indicate the mean scores and percent days (ITT). *Statistically significant difference from placebo as confirmatory results. #Statistically significant difference from placebo for post hoc analysis. JAU, Japanese Allergy Unit; AR, allergic rhinitis; CI, confidence interval; ITT, intention-to-treat; TCRS, total combined rhinitis score

Figure 2 shows the results of immunological responses. Treatment with 10 000 JAU resulted in an increase in *D. farinae*-specific IgE levels after initiating treatment up to week 12 followed by a slight decrease over the treatment period. *D. farinae*-specific IgG_4 levels largely increased in week 12, and a modest increase was observed over the rest of the treatment period. No marked change was seen in the placebo group. *D. pteronyssinus* showed the same results as *D. farinae* (data not shown).

3.3 | Safety

Table 4 shows the summary for safety. No serious ADRs were reported in this trial.

The incidence of AEs among all subjects was slightly higher in the 10 000 JAU group (95.2%) than in the placebo group (87.9%). However, the incidence of moderate AEs was the same in both groups, while severe AEs were only seen in the placebo group. A comparison of AE incidence between pediatric and adolescent subjects showed no major difference except for a lower incidence rate among the adolescent placebo group. ADRs incidences in all subjects across age groups were higher in the 10 000 JAU group than in the placebo group (details on the sequential order of ADRs are available in Table E5 in this article's Online Repository). In both groups, all ADRs were mild or moderate. Predefined significant AEs included investigator-assessed anaphylactic reaction, asthma, AEs leading to discontinuation, and ADRs leading to interruption. No investigator-assessed anaphylactic reactions were observed, whereas asthma was observed in two subjects in the placebo group (both in the pediatric subgroup) and two subjects in the 10 000 JAU group (one pediatric and one adolescent). One pediatric subject in the placebo group had

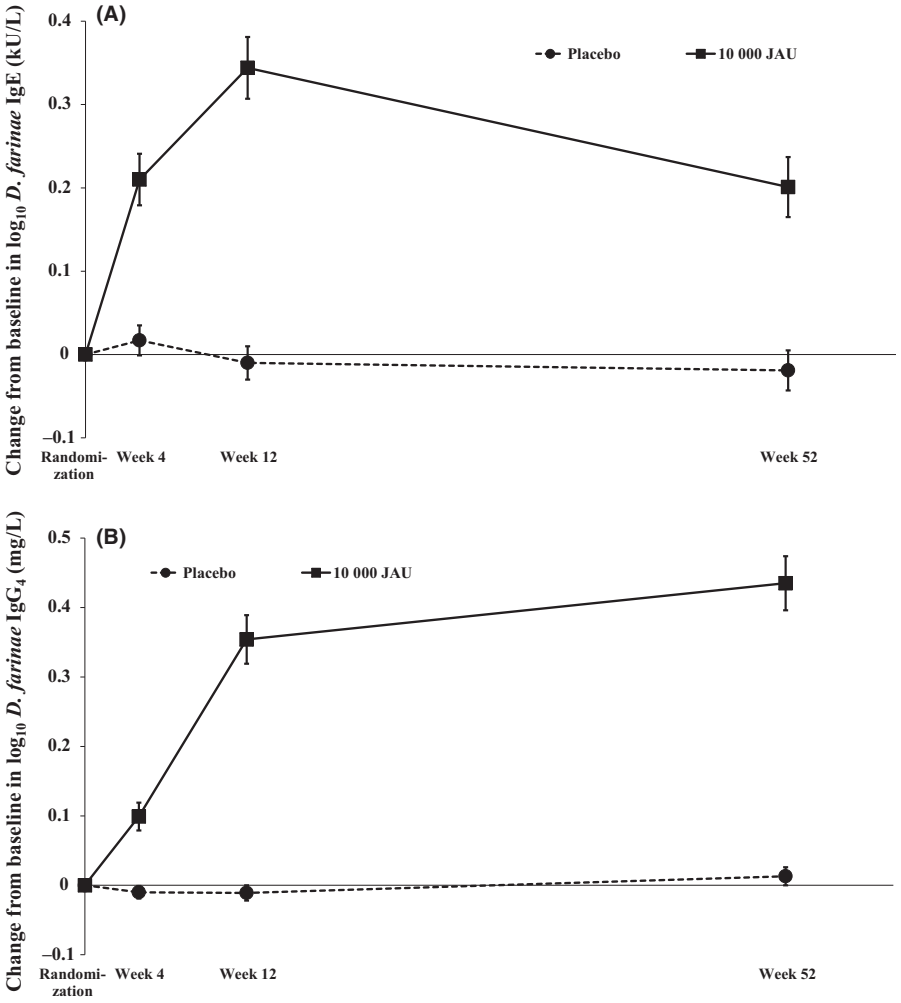

FIGURE 2 Means with 95% CIs of immunologic parameters in the change from baseline levels of *D. farinae* IgE (A) and *D. farinae* IgG_4 (B) throughout the 52-week treatment period (ITT). Means and CIs were calculated using the log_{10}-transformed data. *D. farinae*, *Dermatophagoides farinae*; kU/L, kilo-units per liter; CI, confidence interval; ITT, intention-to-treat

concomitant asthma during randomization. AEs leading to discontinuation and ADRs leading to interruption were more frequent in the active group (nine discontinuations and 12 interruptions) than in the placebo group (five discontinuations and one interruption). This result was more frequently observed in pediatric subjects. Local reactions at the application site, such as mouth swelling, stomatitis, and throat irritation, were the reasons for the interruption in eight of the 12 subjects.

4 | DISCUSSION

This randomized, double-blind, placebo-controlled phase III clinical trial, for the first time, investigated the efficacy of the SQ HDM SLIT-tablet treatment on TCRS in Japanese pediatric and adolescent patients with moderate-to-severe HDM AR. Our findings add to the evidence base established in previous clinical trials using the SQ HDM SLIT-tablet for HDM-induced allergic asthma [17,19] and for HDM AR in adults and adolescents.[18,20-22]

TCRS in the last 8 weeks (FAS), which was the primary endpoint, had an absolute difference of 1.22 between the placebo and 10 000 JAU groups, a relative improvement in relation to placebo of 23% (95% CI: 14% to 31%). These values satisfied the clinical relevance criteria that were the absolute difference with the placebo group of 1 predefined in a previous trial by Demoly et al,[20] and a relative improvement from the placebo group of ≥20% required by the World Allergy Organization[27] and a 95% CI upper limit of ≥10% required by the Food and Drug Administration.[28-30] Furthermore, these results were supported by ITT and PPS analyses. A reduction over time in TCRSs in the placebo group was observed in this trial. This reduction was also reported in previous clinical trials using the SQ HDM SLIT-tablet,[20,21] and other HDM SLIT product.[31] This phenomenon might be caused by sense of expectation for the subjects or their representatives to improvement of symptoms due to participation in the clinical trial. Another reason of this reduction is regression to the mean. In this trial, enrolled subjects were moderate-to-severe AR patients with high rhinitis symptom score. Therefore, these reasons of this reduction might be not different between present and previous trials. In this trial, more than 70% of the subjects were polysensitized to allergens other than HDM, with a skewing trend toward more polysensitized pediatric subjects in the active group than in the placebo group. In our previous trial[21] and the European trial,[20] no difference between monosensitized and polysensitized populations was observed regarding efficacy and safety. In

TABLE 4 Summary of safety assessment

					5-11 years				12-17 years			
	Placebo N = 231		10 000 JAU N = 227		Placebo N = 133		10 000 JAU N = 126		Placebo N = 98		10 000 JAU N = 101	
Treatment group	N	%	N	%	N	%	N	%	N	%	N	%
Serious adverse event (SAE)	3[a]	1.3	1	0.4	2	1.5	–	–	1[a]	1.0	1	1.0
Serious adverse drug reaction	–	–	–	–	–	–	–	–	–	–	–	–
Adverse event (AE)												
All AEs	203	87.9	216	95.2	125	94.0	121	96.0	78	79.6	95	94.1
Mild	168	72.7	183	80.6	101	75.9	102	81.0	67	68.4	81	80.2
Moderate	33	14.3	33	14.5	23	17.3	19	15.1	10	10.2	14	13.9
Severe	2	0.9	–	–	1	0.8	–	–	1	1.0	–	–
Adverse drug reaction (ADR)												
All ADRs	44	19.0	150	66.1	28	21.1	77	61.1	16	16.3	73	72.3
Mild	43	18.6	148	65.2	28	21.1	77	61.1	15	15.3	71	70.3
Moderate	1	0.4	2	0.9	–	–	–	–	1	1.0	2	2.0
Severe	–	–	–	–	–	–	–	–	–	–	–	–
Significant AEs												
Anaphylactic reaction	–	–	–	–	–	–	–	–	–	–	–	–
Asthma	2	0.9	2	0.9	2	1.5	1	0.8	–	–	1	1.0
AEs leading to discontinuation[b]	5[a]	2.2	9	4.0	1	0.8	6[c]	4.8	4[a,d]	4.1	3	3.0
ADRs leading to interruption	1	0.4	12	5.3	–	–	10[c]	7.9	1[d]	1.0	2	2.0

JAU, Japanese Allergy Unit.

[a]A SAE not leading to discontinuation and a non-SAE leading to discontinuation were observed in the same subject.

[b]Includes subjects whose discontinuation was determined by the physicians and those who withdrew their consent due to AEs.

[c,d]One subject in each group temporally interrupted their investigational medicinal product treatment, which was subsequently discontinued due to relapsing ADRs.

addition, Nelson et al reported that efficacy and safety of grass AIT is similar in mono- and polysensitized subjects in the post hoc analysis of pooled data from six trials of the SQ grass SLIT-tablet.[32] This trial provided data on the efficacy of treatment in pediatric patients, regardless of polysensitization to allergens other than HDM. This was consistent with the results of a pooled post hoc analysis from six trials, finding no difference in the efficacy and safety of the grass SLIT-tablet in mono- and polysensitized subjects.[32] In our previous trial in adolescent and adult patients, patients with asthma were excluded.[21] This was due to a potential impact on the AR efficacy assessment. In the present trial, patients with asthma requiring inhaled corticosteroid were excluded to have similar populations except for the age (ie, > Global Initiative for Asthma (GINA) treatment step 1). The efficacy and safety of the SQ HDM SLIT-tablet for the pediatric asthma patient should be investigated in the future.

Similar to our previous trial,[21] hardly any allergy pharmacotherapy was used in the present trial. The TCRS was therefore almost entirely the result of the AR symptom score. This trial also showed that the results for the AR symptom score, the predefined key secondary endpoint, and the TCRS were the same during the primary evaluation period. This finding was comparable with that of a trial in adults and adolescents using another HDM SLIT-tablet, in which pharmacotherapy use was similarly low.[31,33] A statistically significant difference in the AR symptom score between the placebo and 10 000 JAU groups was first noted at week 4 and the difference increased as the treatment period progressed. The onset of efficacy of HDM SLIT-tablet in adults was evident from 12-14 weeks of treatment as confirmed by Demoly and Okubo.[20,21] The present trial suggested that pediatric patients might respond faster to immunotherapy than adults. The sustained AIT-specific efficacy after the completion of long-term treatment, which Durham et al[2,15] have previously confirmed in grass pollen-allergic patients with rhinoconjunctivitis, should be investigated in the future.

TCRS and AR symptom scores, primary and key secondary endpoints, were classified according to pediatric (5 to 11 years) and adolescent (12 to 17 years) subjects. The analysis showed sufficient efficacy in both populations. Berger et al reported that it was possible to differentiate between self and caregivers' assessments in treatment efficacy for children.[34] In this trial, the symptom assessments for pediatric subjects were conducted by their legal representatives to unify assessment. The memorandums were provided to record the symptoms in daytime by the pediatric subjects as needed if their legal representatives were not able to evaluate the daytime symptoms. The final reported data were determined by the legal representatives, and the data recorded by the representatives via e-diary were handled as source data. As a result, no difference between pediatric and adolescent subjects was observed in both endpoints despite assessments by the legal representatives of pediatric subjects. In our

previous trial, we recruited patients aged 12 to 64 years.[21] About 90 adolescents (12 to 17 years) in each group formed the full analysis set (FAS) for the primary endpoint, which was the same as that in the present trial. No major differences in the respective symptom scores of adolescents and adults at baseline were seen in the previous trial, while TCRS results indicated the same efficacy between both populations. Furthermore, both adolescent groups in previous and present trials showed the similar relative differences in TCRS against the placebo groups. Compared with the previous trials with this product, the effect size seems to be similar in adults and children. Thus, both trials together have demonstrated that the SQ HDM SLIT-tablet was efficacious in all patient populations across a wide age range. HDM sensitization, which starts from early childhood, has been revealed to be the greatest risk factor for the onset of asthma in children.[10-14] To date, the use of this drug has been limited to children aged 12 years and older. The results of the present trial suggest that the utility of this drug could increase in clinical practice.

Symptom relief evaluation for AR during the treatment period revealed that the percentage of symptom-severe days decreased, whereas that of symptom-free days increased with increasing treatment duration. These results support the results of the significant improvement of AR symptom score in the active group, which increased with the treatment duration as stated earlier. As a result, significant improvements in symptom relief evaluations of AR and conjunctivitis were seen in the 10 000 JAU group compared with the placebo group during the primary evaluation period, with the exception of the number of symptom-severe days of conjunctivitis, which improved numerically. Significant improvements in the general state of the JRQLQ and global evaluations by the subjects and physicians were observed in the 10 000 JAU group compared with the placebo group, which strongly supported the clinical relevance of the SQ HDM SLIT-tablet.

Both HDM-specific IgE and IgG_4 levels rapidly increased up to week 12. These 2 immunological parameters indicated the contrasting changes later that HDM-specific IgE levels decreased, whereas HDM-specific IgG_4 levels slightly increased. The previous and the present trials show the comparable immunological changes regardless of the differences in populations. Matsuoka et al (to be published in the near future) investigated HDM-specific IgE, IgG_4, and IgE-blocking factors using specimens from trials of the SQ HDM SLIT-tablet conducted in Japan[21] and Europe[19] revealed good consistency between HDM-specific IgE-blocking factors and HDM-specific IgG_4 changes. Although HDM-specific IgG_4 changes have not been fully established as an indicator of efficacy, these findings are consistent with earlier discussions about equivalent efficacy being achievable in a wide age range.

Safety profiles of the SQ HDM SLIT-tablet reported thus far have shown a benign profile, with the present trial reaching a similar conclusion. No investigator-assessed anaphylactic reactions or anaphylaxis by World Allergy Organization systemic allergic reaction grading system[35] were seen, and there was no difference between groups in terms of asthma exacerbation or onset and AEs which could lead to withdrawal from the trial at the physicians' discretion. However, the number of subjects in the pediatric group who discontinued the trial due to AEs seems to be a bit larger than in the adolescent group (six vs three subjects in the active group). Five of the 6 subjects discontinued from the trial by legal representative's decisions caused by headache, rash, nausea, mouth swelling, and oral pruritus/oral mucosal erythema/lip swelling/mouth swelling. Although the subject who experienced mouth swelling needed 7 days to recover the event, two of the five subjects recovered their events within the discontinued day. In addition, other two subjects withdrew from the trial after the AE had recovered because their legal representatives became afraid of relapsing AEs. One subject in the placebo group and 12 subjects in the 10 000 JAU group interrupted the trial treatment due to ADRs. This was more frequent for the pediatric subjects than for adolescents. The majority of the events seen in the 10 pediatric subjects who interrupted their treatment were local events, such as stomatitis, oral discomfort, urticarial, oral pruritus, throat irritation, lip swelling, nausea, and chest and oral pain. Although all of these events were deemed to be mild in severity, the interruptions were decided by the legal representatives of the pediatric subjects. After resuming treatment, one of the 10 subjects developed the same ADR (nausea), which prompted the discontinuation of treatment, while the other nine subjects completed the 52 weeks of treatment. ADRs seen in 2% or more of the subjects in the three age categories (all patients, pediatric subjects, and adolescent subjects) of the 10 000 JAU group were shown according to their frequency. However, no major differences in observed events or their incidences were seen among the three age categories. These findings, in conjunction with those of our previous trial, suggest that in addition to similar efficacy, the SQ HDM SLIT-tablet has a favorable safety profile in HDM AR patients across a wide age range.

In conclusion, the trial revealed the efficacy and favorable safety profile of the SQ HDM SLIT-tablet in Japanese pediatric and adolescent patients with moderate-to-severe HDM AR. Our data demonstrate that the SQ HDM SLIT-tablet can provide beneficial treatment to patients across a wide age range.

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CONFLICT OF INTEREST

K. Masuyama has received consultancy fees from Torii, MSD, GSK, Sanofi, Shionogi, Taiho, and Kyorin; and grants from Torii, MSD, and

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AUTHOR CONTRIBUTION

Keisuke Masuyama, Yoshitaka Okamoto, and Kimihiro Okubo designed this trial and contributed to the interpretation of data. Toru Imai was the safety adviser on this trial. Kazuhiro Okamiya, Ryuji Azuma, Toshiaki Fujinami, Bente Riis, Katsuyo Ohashi-Doi, and Kensuke Natsui participated in the discussion of trial design, conducted the trial, and interpreted the collected data. The original manuscript was drafted by Kazuhiro Okamiya, and all authors gave approval on the submission of the manuscript.

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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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Supplementary text online repository

Title: Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet in Japanese children

Short title: House dust mite sublingual immunotherapy in children

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Fujinami, K. Natsui and K. Ohashi-Doi are employed by Torii. B. Riis is employed by ALK. T. Imai has received consultancy fees from Torii. K. Okubo has received consultancy fees from Torii, Kyowa Hakko Kirin, Teikoku, Hisamitsu, Ono, Taiho, Astellas, MSD, and Mitsubishi Tanabe; and lecture fees from GSK, Sanofi, Shionogi, Kyorin.

Abbreviations

ADR	Adverse drug reaction
AR	Allergic rhinitis
CI	Confidence interval
D. farinae	*Dermatophagoides farinae*
D. pteronyssinus	*Dermatophagoides pteronyssinus*
FAS	Full analysis set
HDM	House dust mite
ITT	Intention-to-treat
JAU	Japanese Allergy Unit
LME	Linear mixed effect
MMRM	Mixed-model repeated measures
PPS	Per-protocol analysis set
SD	Standard deviation

TCRS	Total combined rhinitis score

Methods

Trial population

Main selection criteria included the following:

- Subjects 5 to 17 years of age with a clinical history consistent with moderate-to-severe, persistent, house dust mite (HDM)-induced allergic rhinitis (AR) for at least 1 year prior to informed consent and with AR symptoms despite having received symptomatic treatment.
- Moderate-to-severe HDM AR symptoms during the run-in period, which was defined as an AR symptom score of 7 or more on at least 7 days of the 14-day run-in period without any symptomatic treatment.
- At least 80% of the electronic diary entered during the run-in period.
- Positive nasal provocation test response performed with house dust provocation kit.
- Positive specific IgE levels against *Dermatophagoides pteronyssinus (D. pteronyssinus)*, *Dermatophagoides farinae (D. farinae)*, or both (defined as HDM-specific IgE ≥3.5 kU/L) without 50 kU/L or more of specific IgE against any of the following allergens: cedar, cypress, alder, birch species, cocksfoot, ragweed, mugwort, Japanese hop, cockroach, *Candida* species, *Aspergillus* species, *Alternaria* species, dog dander, or cat dander.
- No clinically relevant history of symptomatic AR caused by any of the following allergens if their specific IgE levels were in the range of 0.7 to less than 50 kU/L: cocksfoot, ragweed, mugwort, Japanese hop, cockroach, *Candida* species, *Aspergillus* species, *Alternaria* species, dog dander, or cat dander.
- Not constantly exposed to a dog and/or a cat (e.g., pet at home), even if a patient has no symptoms with a range of 0.7 to less than 50 kU/L in specific IgE against dog or cat dander.
- No treatment history of bronchial asthma with a corticosteroid within 1 year before the first day of the run-in period.
- No history of anaphylaxis, angioedema, drug allergy, or hypersensitivity to mannitol or gelatin (excipients in the SQ HDM SLIT-tablet).
- No abnormalities in the oral cavity at first administration.

Sample size

Power calculation was based on the data from our previous trial (E1). Mean values of the square root of total combined rhinitis score (TCRS) in the primary evaluation period were 2.25 in the placebo group, 1.99 in the 10,000 Japanese Allergy Unit (JAU) group, and 2.03 in the 20,000 JAU group; the combined standard deviation (SD) was 0.77. The mean value of the square root of baseline AR symptom score was 2.90 and the combined SD was 0.22. The correlation coefficient between TCRS in the primary evaluation period and the baseline AR symptom score was 0.23. For each simulation pattern, random numbers were generated on the basis of bivariate normal distribution of TCRS in the primary evaluation period and the baseline AR symptom score. A linear mixed effects (LME) model for TCRS in the primary evaluation period was used for analyses. A Monte Carlo simulation was performed using analysis sets consisting of 100, 130, 150, 180, or 200 subjects from each group. Results suggested that an analysis set consisting of at least 180 subjects from each group allows efficacy verification even if the responsiveness of subjects aged 5 to 17 years of age varies with age and increases variability (**Table E1**). The target number of randomized subjects was set at 200 in each group with a 10% discontinuation rate that showed in our previous trial. The relative difference in TCRS compared with that in placebo after back-transformation of both square-rooted TCRSs indicated that approximately 20% corresponded to the World Allergy

Organization recommendation (E2) as the minimum difference with clinical significance between the active and placebo groups.

Statistical methodology

All statistical tests were performed using SAS version 9.3 software (SAS Institute, Cary, NC) with a 5% significance level, and all tests and 95% confidence intervals (CIs) were two-sided.

The primary end point was TCRS in the last 8 weeks of the 52-week treatment period (primary evaluation period). The key secondary end point was AR symptom score in the primary evaluation period. The same analytic methods were performed for both end points.

The primary efficacy analysis was based on an LME model adopting the AR symptom score at baseline and the treatment group as fixed effects and the clinical site as a random effect with full analysis set (FAS). Square root transformation was performed for TCRS (primary end point) and AR symptom score (key secondary end point) in the primary evaluation period as a dependent variable and the AR symptom score at baseline as a covariate. The primary outcome was the pairwise comparison between treatment groups using a *t*-test in the LME model. CIs for ratios of adjusted mean values between treatment groups were calculated using the Fieller theorem (E3). Back transformation was performed for output results of the square root of the variables to indicate adjusted mean values, difference in adjusted mean values between treatment groups, ratios of

adjusted mean values between treatment groups, and CIs.

Additional analyses included the same LME model on the per-protocol analysis set (PPS) and mixed-model repeated measures (MMRM) methods on the intention-to-treat (ITT) population. For MMRM, the variance structure was unstructured correlation, and the computation method for covariance matrices of fixed effects was a robust (sandwich) covariance matrix estimator.

The same analysis as the primary analysis was performed for age subgroups, except that the clinical site as a random effect was not included in the analysis model because the subgroups differed in the number of clinical sites.

Other symptom and medication scores were analyzed by the same LME model with appropriate changes in dependent variables and covariates. Symptom-free days were defined as those when all symptoms were scored 0, and symptom-severe days were those when at least 1 symptom was scored 3. For these, intergroup paired comparison evaluated by logistic regression was performed in the presence or absence of relevant days in the primary evaluation period (0, 1 variable) as a dependent variable, and the square-rooted AR symptom score at baseline and the treatment group as fixed effects. The *t*-test was performed to determine the mean days of symptom-free and symptom-severe day evaluation. Japanese Rhinoconjunctivitis Quality of Life Questionnaire scores and global evaluation were analyzed using the Wilcoxon rank sum test.

Results

Population

Table E2 shows stratified baseline symptom scores divided into pediatrics (5 to 11 years) and adolescents (12 to 17 years) (FAS). There was no difference between the two populations in each group.

Symptom score

Table E3 show that the change from baseline in allergic rhinitis symptom scores in the placebo and 10,000 JAU groups increased as the treatment progressed, and the difference of change from baseline between the placebo and 10,000 JAU increase as the progressed.

Table E4 shows that all rhinitis and conjunctivitis symptom scores in the 10,000 JAU group significantly decreased when compared with those of the placebo group during the primary evaluation period (weeks 44–52).

Safety

Table E5 shows the sequential order of adverse drug reactions (ADRs) in the 10,000 JAU group reported by 2% or more of subjects. Most of the events were the same local reactions at the

application sites in both populations; thus, there was no difference in safety profile between pediatrics and adolescents.

References

E1 Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. *J Allergy Clin Immunol* 2017;**139**:1840-8.e10.

E2 Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy World Allergy Organization position paper 2009. *World Allergy Organ J* 2009;**2**:233-81.

E3 Fieller EC. Some problems in interval estimation. *J Roy Stat Soc B* 1954;**16**:175-85.

Online Repository Figure Legends

Figure E1: Trial design. Subjects should follow an up-dosing regimen at the beginning of treatment period. The e-diary collected 14 days of data during the run-in period and 5 times after up-dosing until the initiation of the primary evaluation period, comprising the last 8 weeks of the treatment period. Black boxes represent the e-diary periods.

JAU, Japanese Allergy Unit; e-diary, electronic diary

Figure E2: Subject disposition. *One subject who satisfied the FAS definition, the completion of e-diary at least 80% during the primary evaluation period, was included in FAS.

JAU, Japanese Allergy Unit; AE, adverse event; FAS, full analysis set

Table E1. Power for statistical analysis

Pattern	TCRS in the primary evaluation period		Power (%)				
	Placebo group	10,000 JAU group	Number of subjects in each group for primary analysis				
	Mean (SD)	Mean (SD)	100	130	150	180	200
1	2.25 (0.77)	2.00 (0.77)	65	76	82	88	92
2	2.25 (0.85)	2.00 (0.85)	56	67	74	81	85
3	2.25 (0.95)	2.00 (0.95)	47	58	64	72	77

Power calculation was based on the data from our previous trial.[E1]

TCRS, total combined rhinitis score; JAU, Japanese Allergy Unit; SD, standard deviation

Table E2. Comparison of baseline symptom scores in pediatrics and adolescents (FAS)

Symptom score	Pediatrics (5–11 years)		Adolescents (12–17 years)	
	Placebo N = 129	10,000 JAU N = 118	Placebo N = 89	10,000 JAU N = 91
Runny nose	2.22 ± 0.41 2.14 (0.9–3.0)	2.26 ± 0.41 2.21 (1.4–3.0)	2.31 ± 0.45 2.29 (1.0–3.0)	2.28 ± 0.41 2.21 (1.1–3.0)
Blocked nose	2.07 ± 0.51 2.07 (0.1–3.0)	2.17 ± 0.49 2.00 (1.1–3.0)	2.19 ± 0.53 2.08 (1.0–3.0)	2.16 ± 0.47 2.14 (1.1–3.0)
Sneezing	2.07 ± 0.43 2.00 (0.8–3.0)	2.03 ± 0.52 2.00 (1.0–3.0)	2.15 ± 0.53 2.07 (0.4–3.0)	2.01 ± 0.49 2.00 (1.1–3.0)
Itchy nose	2.06 ± 0.50 2.00 (0.4–3.0)	2.10 ± 0.52 2.00 (0.9–3.0)	2.13 ± 0.55 2.00 (0.1–3.0)	2.04 ± 0.52 2.00 (0.9–3.0)
AR symptom score	8.43 ± 1.26 8.36 (6.3–12.0)	8.56 ± 1.44 8.21 (5.9–12.0)	8.78 ± 1.53 8.43 (6.4–12.0)	8.49 ± 1.37 8.14 (6.4–12.0)
Gritty feeling/ Red/Itchy eyes	1.23 ± 0.71 1.21 (0.0–2.9)	1.27 ± 0.70 1.29 (0.0–3.0)	1.20 ± 0.81 1.21 (0.0–3.0)	1.18 ± 0.69 1.07 (0.0–2.6)
Watery eyes	0.82 ± 0.66 0.93 (0.0–2.6)	0.76 ± 0.69 0.71 (0.0–2.9)	0.86 ± 0.79 0.79 (0.0–3.0)	0.79 ± 0.66 0.79 (0.0–2.6)
Conjunctivitis symptom score	2.05 ± 1.29 2.07 (0.0–5.4)	2.02 ± 1.30 1.96 (0.0–5.8)	2.07 ± 1.53 2.07 (0.0–6.0)	1.97 ± 1.27 1.79 (0.0–5.2)

Results are presented as mean ± standard deviation or median (minimum–maximum value).
FAS, full analysis set; JAU, Japanese Allergy Unit; AR, allergic rhinitis

Table E3. The change from baseline in AR symptom scores at each evaluation period for *post hoc* analysis (FAS)

	Treatment group	N	AR symptom score			*P* value*
			Mean	Change from baseline (%)	Difference from placebo	
Baseline	Placebo	218	8.57	–	–	–
	10,000 JAU	209	8.53	–	–	–
Week 4-6	Placebo	218	7.50	-1.07 (-12.5)	–	–
	10,000 JAU	209	7.14	-1.39 (-16.3)	-0.32	0.0854
Week 12-14	Placebo	218	6.70	-1.87 (-21.8)	–	–
	10,000 JAU	209	6.09	-2.44 (-28.6)	-0.57	0.0129
Week 20-22	Placebo	218	6.54	-2.03 (-23.6)	–	–
	10,000 JAU	209	5.82	-2.71 (-31.8)	-0.69	0.0057
Week 28-30	Placebo	218	6.19	-2.38 (-27.7)	–	–
	10,000 JAU	209	5.48	-3.05 (-35.8)	-0.67	0.0078
Week 36-38	Placebo	218	5.53	-3.05 (-35.5)	–	–
	10,000 JAU	209	4.67	-3.86 (-45.2)	-0.81	0.0016
Week 44-52	Placebo	218	5.45	-3.12 (-36.4)	–	–
	10,000 JAU	209	4.35	-4.18 (-49.0)	-1.06	<0.0001

*: t-test

AR, allergic rhinitis; FAS, full analysis set; JAU, Japanese Allergy Unit

Table E4. Separate symptom scores during the primary evaluation period (weeks 44–52) (FAS)

Symptom	Treatment group	N	Linear mixed effect*		
			Adjusted mean	Absolute difference from placebo (95% CI)	*P* value
Runny nose	Placebo	218	1.38	–	–
	10,000 JAU	209	1.08	0.29 (0.15 to 0.43)	<0.001
Blocked nose	Placebo	218	1.22	–	–
	10,000 JAU	209	0.87	0.35 (0.20 to 0.50)	<0.001
Sneezing	Placebo	218	1.23	–	–
	10,000 JAU	209	0.97	0.26 (0.14 to 0.39)	<0.001
Itchy nose	Placebo	218	1.08	–	–
	10,000 JAU	209	0.84	0.25 (0.10 to 0.39)	0.001
Gritty feeling/ Red/Itchy eyes	Placebo	218	0.52	–	–
	10,000 JAU	209	0.34	0.18 (0.08 to 0.28)	<0.001
Watery eyes	Placebo	218	0.24	–	–
	10,000 JAU	209	0.13	0.11 (0.05 to 0.18)	<0.001

* Fixed effect: each symptom score at baseline and the treatment group, Random effect: clinical site
FAS, full analysis set; CI, confidence interval; JAU, Japanese Allergy Unit

Table E5. Comparison of the sequential order of ADRs reported by 2% or more of subjects in the 10,000 JAU group

All subjects N = 227			Pediatrics (5–11 years) N = 126			Adolescents (12–17 years) N = 101		
ADRs	N	(%)	ADRs	N	(%)	ADRs	N	(%)
Oral pruritis	51	(22.5)	Oral pruritis	27	(21.4)	Oral pruritis	24	(23.8)
Mouth edema	29	(12.8)	Mouth edema	15	(11.9)	Throat irritation	15	(14.9)
Throat irritation	27	(11.9)	Throat irritation	12	(9.5)	Mouth edema	14	(13.9)
Mouth swelling	22	(9.7)	Mouth swelling	12	(9.5)	Mouth swelling	10	(9.9)
Oral discomfort	20	(8.8)	Oral discomfort	10	(7.9)	Oral discomfort	10	(9.9)
Ear pruritus	15	(6.6)	Tongue pruritus	8	(6.3)	Ear pruritus	9	(8.9)
Lip swelling	13	(5.7)	Lip swelling	8	(6.3)	Larynx discomfort	7	(6.9)
Oropharyngeal discomfort	12	(5.3)	Stomatitis	8	(6.3)	Oropharyngeal discomfort	7	(6.9)
Larynx discomfort	11	(4.8)	Ear pruritus	6	(4.8)	Lip swelling	5	(5.0)
Tongue pruritus	10	(4.4)	Oral mucosal erythema	6	(4.8)	Paresthesia oral	4	(4.0)
Stomatitis	10	(4.4)	Oropharyngeal discomfort	5	(4.0)	Eczema	3	(3.0)
Paresthesia oral	9	(4.0)	Paresthesia oral	5	(4.0)	Stomatitis	2	(2.0)
Oral mucosal erythema	7	(3.1)	Dyspnea	4	(3.2)	Cough	2	(2.0)
			Glossitis	4	(3.2)	Pruritus	2	(2.0)
			Larynx discomfort	4	(3.2)	Rash	2	(2.0)
						Hypoesthesia oral	2	(2.0)
						Tongue pruritus	2	(2.0)
						Lip pruritus	2	(2.0)

JAU, Japanese Allergy Unit; ADRs, adverse drug reactions

Figure E1

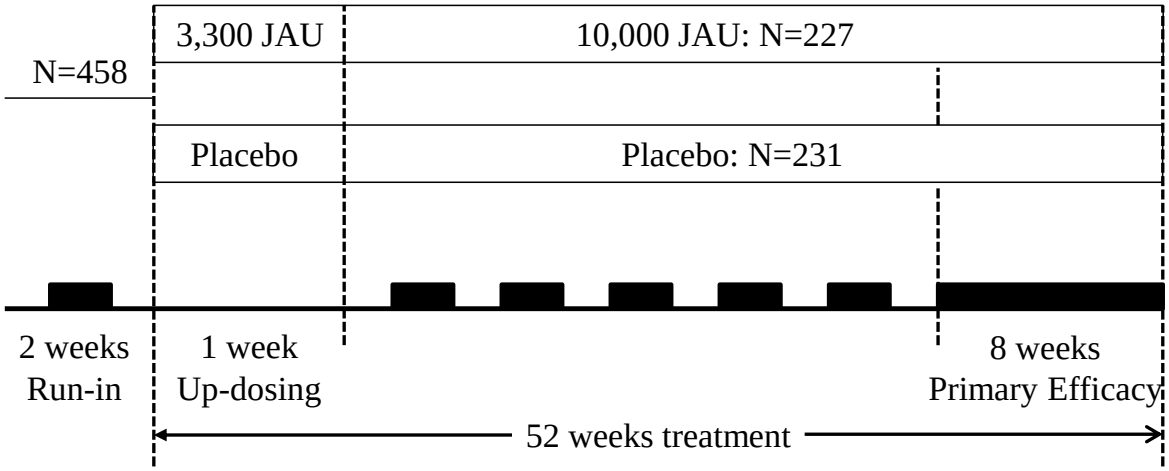
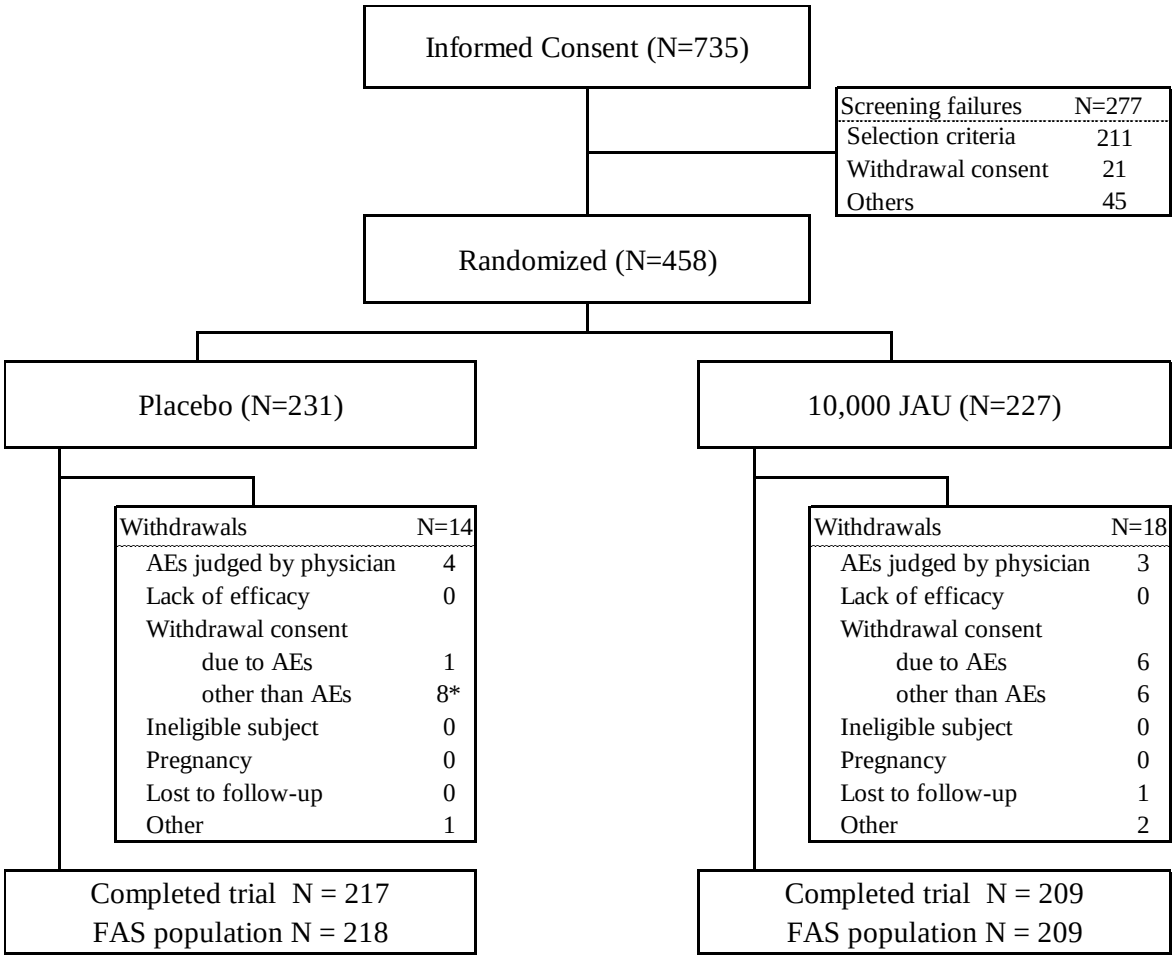

3,300 JAU
10,000 JAU: N=227
N=458
Placebo
Placebo: N=231
2 weeks
Run-in
1 week
Up-dosing
8 weeks
Primary Efficacy
52 weeks treatment

Figure E2


Informed Consent (N=735)
Screening failures N=277
Selection criteria 211
Withdrawal consent 21
Others 45
Randomized (N=458)
Placebo (N=231)
10,000 JAU (N=227)
Withdrawals N=14
AEs judged by physician 4
Lack of efficacy 0
Withdrawal consent
due to AEs 1
other than AEs 8*
Ineligible subject 0
Pregnancy 0
Lost to follow-up 0
Other 1
Withdrawals N=18
AEs judged by physician 3
Lack of efficacy 0
Withdrawal consent
due to AEs 6
other than AEs 6
Ineligible subject 0
Pregnancy 0
Lost to follow-up 1
Other 2
Completed trial N = 217
FAS population N = 218
Completed trial N = 209
FAS population N = 209