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Original Article

Safety profile and immunological response of dual sublingual immunotherapy with house dust mite tablet and Japanese cedar pollen tablet

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ABSTRACT

Background: There have been no studies of dual administration of sublingual immunotherapy (SLIT) tablets for perennial and seasonal allergic rhinitis. This trial (JapicCTI-184014) was conducted to investigate the safety profile and immunological response during dual therapy with SQ house dust mite (HDM) and Japanese cedar pollen (JCP) SLIT tablets.

Methods: This was a multicenter, open-label, randomized trial of 109 Japanese patients with coexisting HDM and JCP allergic rhinitis who had positive tests for HDM- and JCP specific IgE (≥ 0.7 kU/L). Patients were allocated to receive HDM (N = 54) or JCP (N = 55) SLIT tablets alone for 4 weeks followed by 8 weeks of dual therapy with both SLIT tablets administered within 5 min of each other. Adverse events (AEs), adverse drug reactions (ADRs), and serum IgE and IgG4 specific for HDM (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*) and JCP were recorded.

Results: The percentage of subjects with AEs and ADRs was similar between the two groups and between the two periods of monotherapy and dual therapy. Most AEs and ADRs were mild in severity, and no serious events were observed. The most common ADRs were local events in the oral cavity. Levels of IgE

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Abbreviations:

AE, Adverse event; ADR, Adverse drug reaction; AR, Allergic rhinitis; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*; HDM, House dust mite; JAU, Japanese allergy units; JCP, Japanese cedar pollen; SD, Standard deviation; SLIT, Sublingual immunotherapy

and IgG4 specific for HDM (*D. farinae*, *D. pteronyssinus*) and JCP were increased after treatment with HDM and JCP SLIT tablets, respectively.

Conclusions: Dual therapy with both SLIT tablets administered within 5 min after 4 weeks of monotherapy with HDM or JCP tablet was well tolerated and induced the expected immunological responses.

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Introduction

HDMs are prevalent worldwide and are the principal cause of perennial allergic rhinitis. In Japanese nationwide survey, the reported prevalence of perennial allergic rhinitis is 23.4% in 2008.¹ In contrast, region-specific pollens are the main causes of seasonal allergic rhinitis; in Japan, the most common pollinosis is caused by Japanese cedar pollen (JCP) and has a reported prevalence of 26.5%.¹ Japanese cedar pollinosis is considered the national affliction in Japan,² and some epidemiological surveys reported that the prevalence of Japanese cedar pollinosis is 36.7% and 45.6%.^{3,4} The nationwide survey indicates the increasing prevalence of perennial allergic rhinitis and Japanese cedar pollinosis in 2008 compared with in 1998.¹ SLIT products have been developed in Japan for the treatment of HDM allergic rhinitis and Japanese cedar pollinosis and both are currently in clinical use.^{5–10}

Many patients with allergic rhinitis are sensitized to multiple allergens,¹¹ and there is some clinical evidence to support simultaneous use of multiple allergens for subcutaneous immunotherapy.¹² Although the efficacy and safety of individual SLIT tablets for each allergic rhinitis have been well-characterized, relatively little is known about the efficacy and safety of dual SLIT tablets and there are only limited clinical data on concomitant treatment of two distinct allergies with SLIT tablets. One North American study examined the outcomes of sequential and simultaneous treatment with SLIT tablets for grass and ragweed seasonal allergic rhinitis.¹³ Two other studies in Japan examined the safety of JCP SLIT drops (a liquid formulation) and SQ HDM SLIT tablets for coexisting allergies to the perennial allergen HDM and the seasonal allergen JCP.^{14,15} However there are no studies of dual therapy with SLIT tablets for perennial and seasonal allergic rhinitis. Here, we report the results of a trial of dual SLIT tablet therapy for HDM and JCP allergic rhinitis, the most common coexisting perennial and seasonal allergic rhinitis in Japan.³

The trial was conducted to investigate the safety profile and immunological response of Japanese patients with coexisting HDM and JCP allergic rhinitis. Patients received 4 weeks of monotherapy with either SQ HDM or JCP SLIT tablet followed by 8 weeks dual therapy with both tablets administered to patients within 5 min of each other.

Methods**Trial design**

This was a multicenter, open-label, randomized trial (JapicCTI-184014) performed between July and December 2018, which is outside the usual JCP dispersal season of February to April. A total of 109 Japanese patients with coexisting HDM and JCP allergic rhinitis were enrolled at 14 sites in Japan and were randomized to receive either HDM (N = 54) or JCP (N = 55) SLIT tablet for 4 weeks (HDM-first and JCP-first groups, respectively), with both groups then

receiving dual therapy for an additional 8 weeks. The trial design is shown in Figure 1. SQ HDM SLIT tablets were administered at an initial dose of 3300 Japanese allergy units (JAU) for 1 week followed by a maintenance dose of 10,000 JAU thereafter (see below for details of tablet formulations). This is the approved dose in Japan, whereas the approved dose in the US and Europe is 12 SQ HDM equivalent to 20,000 JAU. JCP SLIT tablets were administered at an initial dose of 2000 JAU for 1 week and a maintenance dose of 5000 JAU thereafter. The durations of 4 and 8 weeks for monotherapy (referred to as Period 1) and dual therapy (Period 2), respectively, were based on the results of two previous trials of the same SQ HDM SLIT tablet^{5,6} and one trial of the same JCP SLIT tablet,¹⁰ which showed prevalences of adverse drug reactions (ADRs) of 75.9%, 76.6%, and 84.0%, respectively, within 4 weeks of treatment. In all three trials, ADRs tended to decline from week 5 onwards. This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice requirements and was approved by the Institutional Review Board of each trial site. Written informed consent was obtained from all patients or from a legal representative for patients who were minors before starting the trial.

Study population

A total of 109 patients (aged 6–57 years) with coexisting HDM and JCP allergic rhinitis were enrolled between July and September 2018. The inclusion criteria were: positive test for IgE specific for HDM (*Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*) and JCP (≥ 0.7 kU/L), positive nasal provocation test (house dust), and moderate or more severe¹ symptoms of Japanese cedar pollinosis for a period of at least 1 week during both of the preceding two JCP seasons in 2017 and 2018. The main exclusion criteria were: history of allergen immunotherapy with a drug containing an HDM or JCP ingredient, coexisting severe bronchial asthma,^{16,17} coexisting food allergies, coexisting drug allergies, coexisting oral allergy syndrome, treatment for a coexisting malignant tumor within the previous 5 years, coexisting autoimmune disease or immunodeficiency disease, and coexisting or history of hypersensitivity to mannitol or gelatin additives used in the tablets.

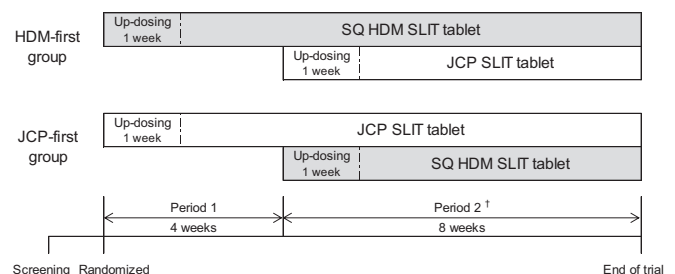


Fig. 1. Trial design. HDM, house dust mite; SLIT, sublingual immunotherapy; JCP, Japanese cedar pollen. [†] First and second tablets administered within 5 min.

Patients with a history of treatment with steroid hormone preparations, immunosuppressants, or antibody drugs with systemic effects within 90 days of the planned starting date were also excluded.

Treatment

The SQ HDM SLIT tablets (MITICURE®; Torii, Tokyo, Japan; manufactured by ALK-Abelló, Hørsholm, Denmark) and JCP SLIT tablets (CEDARCURE®, Torii) are fast-dissolving freeze-dried tablets and were provided by Torii, the trial sponsor. SQ HDM SLIT tablets contained allergen extracts derived from *D. farinae* and *D. pteronyssinus* at a 1:1 ratio. Both the SQ HDM and JCP SLIT tablets available in Japan can be administered at an initial dose for 1 week and a maintenance dose thereafter. In this study, during Period 1, patients received one tablet daily sublingually for 1 min before swallowing. The initial dose was administered for 1 week followed by a maintenance dose for 3 weeks. During Period 2, the first tablet was held sublingually for 1 min before swallowing, and then the second tablet was administered within 5 min of the first and held sublingually for 1 min before swallowing. The initial dose was administered for 1 week followed by maintenance dose for 7 weeks. Tablets were administered at the trial site on the first day of Periods 1 and 2 and subjects remained under physician observation for at least 30 min to ensure safety. Patients were asked to refrain from rinsing the mouth or eating/drinking for 5 min after taking the tablet(s). They were prohibited from concomitant use of steroids, antihistamines, leukotriene receptor antagonists, and immunosuppressive agents with systemic effects throughout the trial; however, these agents could be used if judged necessary by an investigator to treat an ADR or adverse event (AE). Use of inhaled steroids and leukotriene receptor antagonists was permitted for bronchial asthma provided that the dosage and regimen remained constant.

Assessments

Subjects or their legal representatives (for minors) recorded the subject's symptoms in a diary. During visits to the trial sites, physicians reviewed the diary for occurrences of AEs and ADRs. AEs were defined and evaluated using MedDRA/J v21.1. ADRs were defined as AEs deemed to be related to the drug. For all subjects, hematology and blood biochemistry analyses were performed with samples taken at screening and 12 weeks (end of treatment). For subjects aged 12 years and older, blood samples for immunological tests were collected at screening, randomization and after 4 weeks (the first day of dual SLIT therapy), 8 weeks, and 12 weeks (end of treatment). For subjects younger than 12 years of age, blood samples were collected only at screening (for testing of IgE levels required for inclusion) to avoid excessive blood collection. Serum samples were assayed for *D. farinae* specific, *D. pteronyssinus* specific, and JCP specific IgE and IgG4. Immunological response was tested by the general linear model for repeated measures includes the common logarithms values as the dependent variable, visit as fixed effect, with unstructured covariance structure for within-patient correlation. Multiplicity was adjusted by Dunnett type method.

Sample size calculation

A sample size of 50 subjects in each treatment group was planned to compare the percentage of subjects with ADRs between groups. Assuming the percentage of subjects with ADR of 60% in

each treatment group during Period 2 based on the authors' previous studies,^{5,6,10} a sample size of 50 subjects in each treatment group allowed for accuracy of the percentage of subjects with ADRs with a one-sided 95% confidence interval width of 13.6% (46.4–73.6%). A sample size of 50 subjects also provides a 90% or higher possibility of events that occur with 5% the percentage of subjects with ADRs being detected at least once. All analyses were conducted using SAS software version 9.3.

Results

Patient characteristics

Informed consent was obtained from 123 patients and a total of 109 subjects were enrolled; 54 were randomized to the HDM-first group and 55 to the JCP-first group (Fig. 2). Three subjects discontinued the trial due to AEs. Thus, 52 (96.3%) and 54 (98.2%) subjects in the HDM-first and JCP-first groups, respectively, completed the trial. The baseline characteristics of the study cohort and the two groups are shown in Table 1. There were no major differences in the characteristics between the two groups.

Adverse events and adverse drug reactions

A summary of the AEs and ADRs is shown in Table 2. None of the AEs met the regulatory definition of a serious AE. Nearly all of the AEs and ADRs observed in both periods were mild, and none were deemed to be severe. Over the entire 12-week trial, the percentage of subjects with AEs was 81.5% and 90.9% and the percentage with ADRs was 74.1% and 78.2% in the HDM-first and JCP-first groups, respectively. There were no significant differences between groups. A causal relationship with first tablet in each group was not-related in some AEs in Period 2, but a causal relationship with second tablet was always related in Period 2. The percentage of subjects with ADRs in Period 1 was higher than that in Period 2 in the HDM-first group but they were similar in both periods in the JCP-first group. Of the three ADR-related discontinuations, two occurred in the HDM-first group (one each in Periods 1 and 2), and one in the JCP-first group (in Period 2). Treatment was interrupted due to ADRs in Periods 1 and 2 in 1 and 2 patients, respectively, in the HDM-first group, and in 2 and 1 patients, respectively, in the JCP-first group.

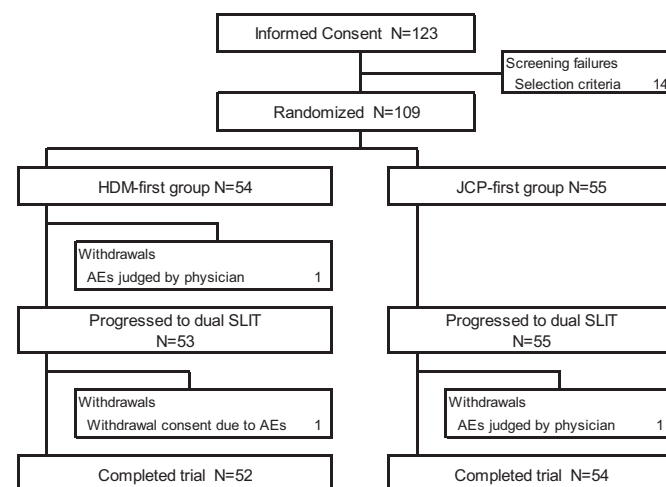


Fig. 2. Subject disposition. HDM, house dust mite; SLIT, sublingual immunotherapy; JCP, Japanese cedar pollen.

Table 1
Baseline characteristics and demography.

Treatment group	HDM-first group (N = 54)	JCP-first group (N = 55)	Overall (N = 109)
Male, no (%)	32 (59.3)	30 (54.5)	62 (56.9)
Age (y)			
Mean $\pm$ SD	20.9 $\pm$ 13.7	24.8 $\pm$ 15.0	22.9 $\pm$ 14.4
Median (Minimum – Maximum)	13.0 (6–50)	19.0 (6–57)	16.0 (6–57)
Years with HDM AR (y)			
Mean $\pm$ SD	10.5 $\pm$ 9.4	11.5 $\pm$ 9.3	11.0 $\pm$ 9.4
Median (Minimum – Maximum)	7.5 (0–35)	10.0 (0–44)	8.0 (0–44)
Years with Japanese cedar pollinosis (y)			
Mean $\pm$ SD	7.8 $\pm$ 6.9	12.0 $\pm$ 9.2	10.0 $\pm$ 8.4
Median (Minimum – Maximum)	5.5 (1–30)	10.0 (2–44)	7.0 (1–44)
<i>D. farinae</i> specific IgE (kU/L), no. (%)			
<17.5	19 (35.2)	19 (34.5)	38 (34.9)
≥ 17.5 to <50	9 (16.7)	16 (29.1)	25 (22.9)
≥ 50 to <100	14 (25.9)	7 (12.7)	21 (19.3)
≥ 100	12 (22.2)	13 (23.6)	25 (22.9)
Mean $\pm$ SD	88.80 $\pm$ 119.37	90.61 $\pm$ 140.06	89.71 $\pm$ 129.63
Median (Minimum – Maximum)	42.65 (0.7–549.0)	38.00 (0.4–816.0)	38.80 (0.4–816.0)
<i>D. pteronyssinus</i> specific IgE (kU/L), no. (%)			
<17.5	18 (33.3)	21 (38.2)	39 (35.8)
≥ 17.5 to <50	11 (20.4)	13 (23.6)	24 (22.0)
≥ 50 to <100	13 (24.1)	8 (14.5)	21 (19.3)
≥ 100	12 (22.2)	13 (23.6)	25 (22.9)
Mean $\pm$ SD	84.24 $\pm$ 108.85	92.54 $\pm$ 158.27	88.43 $\pm$ 135.49
Median (Minimum – Maximum)	40.60 (0.1–461.0)	27.80 (0.7–838.0)	31.40 (0.1–838.0)
JCP specific IgE (kU/L), no. (%)			
<17.5	18 (33.3)	10 (18.2)	28 (25.7)
≥ 17.5 to <50	14 (25.9)	21 (38.2)	35 (32.1)
≥ 50 to <100	7 (13.0)	11 (20.0)	18 (16.5)
≥ 100	15 (27.8)	13 (23.6)	28 (25.7)
Mean $\pm$ SD	97.08 $\pm$ 123.22	92.80 $\pm$ 108.66	94.92 $\pm$ 115.58
Median (Minimum – Maximum)	41.30 (1.2–488.0)	44.10 (0.8–383.0)	44.10 (0.8–488.0)

HDM, house dust mite; JCP, Japanese cedar pollen; SD, standard deviation; AR, allergic rhinitis; kU/L, kilo-units per liter; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*.

Table 3 lists the ADRs reported by 5% or more of subjects in total. During both periods and in both treatment groups, the main ADRs were oral cavity events, including mouth swelling, oral pruritus, and throat irritation.

Figure 3 shows the cumulative percentage of subjects with ADRs and the weekly and cumulative number of ADRs throughout the trial. The cumulative percentage of subjects with ADR was higher in the HDM-first group than the JCP-first group for the first 3–4 weeks of the trial (i.e., during monotherapy); was then higher in the JCP-first group than the HDM-first group for the next 4 weeks (i.e., the first half of dual therapy); and became approximately equal for both groups in the final 4 weeks of dual therapy.

The weekly number of ADRs was larger in the HDM-first group compared with the JCP-first group, in weeks 1–2, but was similar in weeks 3–4. Conversely, the weekly number of ADRs during weeks 5–6 (weeks 1–2 after starting dual SLIT therapy) were larger in the JCP-first group compared with the HDM-first group, but they were similar from week 7 onwards (third week since starting dual SLIT).

The cumulative number of ADRs was higher in the HDM-first group than the JCP-first group, up to week 4, but was similar during dual therapy.

Figure 4 shows the change in immunological response (*D. farinae* specific and JCP specific IgE and IgG4) during the trial. In the HDM-first group, *D. farinae* specific IgE and IgG4 levels significantly increased from baseline in all period, and JCP specific IgE and IgG4 levels also significantly increased during dual therapy. A similar trend was observed for the JCP-first group, however, *D. farinae* specific IgE at week 4 significantly increased, despite not starting dual therapy with SQ HDM SLIT tablet. Levels of

D. pteronyssinus specific IgE and IgG4 followed a similar course to that of *D. farinae* specific IgE and IgG4 (data not shown).

Discussion

In Japan, many patients with allergic rhinitis have coexisting allergies to the perennial allergen HDM and the seasonal allergen JCP.³ In an ideal situation, treatment of both allergies concomitantly would considerably shorten the duration of treatment; however, there have been no studies to date on the safety or efficacy of dual SLIT tablet therapy in Japan. One recent North American trial of dual SLIT tablet therapy for coexisting grass and ragweed seasonal allergic rhinitis observed good tolerability.¹³ Therefore, we investigated the safety profile and immunological response of patients with coexisting HDM and JCP allergic rhinitis during dual SLIT tablet therapy.

We found that nearly all AEs and ADRs reported in this trial were mild in severity, and most ADRs were local events in the oral cavity. Three subjects discontinued treatment due to ADRs, and nearly all other ADR-related treatment interruptions were transient. These results are comparable to those of previous studies examining monotherapy with SQ HDM or JCP SLIT tablets.^{5,6,10} We also found that the percentage of subjects with ADRs, number of ADRs, and type of ADRs were comparable between the HDM-first and JCP-first groups. We did observe between-group differences in the cumulative percentage of subjects with ADRs up to week 7 and in the cumulative number of ADRs up to week 4, but both were similar thereafter.

The treatment phase of the North American study¹³ cited above was 6 weeks: 2 weeks of monotherapy with grass SLIT tablet; 2

Table 2

Summary of safety.

Treatment group		All Period			Period 1			Period 2		
		E	N	(%)	E	N	(%)	E	N	(%)
HDM-first group										
Serious AEs		0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
All AEs		257	44	(81.5)	111	38	(70.4)	146	36	(67.9)
Severity	Mild	254	41	(75.9)	109	36	(66.7)	145	35	(66.0)
	Moderate	3	3	(5.6)	2	2	(3.7)	1	1	(1.9)
	Severe	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
leading to discontinuation		3	2	(3.7)	1	1	(1.9)	2	1	(1.9)
leading to interruption		9	8	(14.8)	2	2	(3.7)	7	6	(11.3)
All ADRs		183	40	(74.1)	88	35	(64.8)	95	28	(52.8)
Severity	Mild	183	40	(74.1)	88	35	(64.8)	95	28	(52.8)
	Moderate	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
	Severe	3	2	(3.7)	1	1	(1.9)	2	1	(1.9)
leading to discontinuation		3	3	(5.6)	1	1	(1.9)	2	2	(3.8)
JCP-first group										
Serious AEs		0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
All AEs		269	50	(90.9)	102	44	(80.0)	167	41	(74.5)
Severity	Mild	265	46	(83.6)	101	43	(78.2)	164	38	(69.1)
	Moderate	4	4	(7.3)	1	1	(1.8)	3	3	(5.5)
	Severe	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
leading to discontinuation		1	1	(1.8)	0	0	(0.0)	1	1	(1.8)
leading to interruption		8	6	(10.9)	4	3	(5.5)	4	3	(5.5)
All ADRs		189	43	(78.2)	66	35	(63.6)	123	38	(69.1)
Severity	Mild	187	41	(74.5)	65	34	(61.8)	122	37	(67.3)
	Moderate	2	2	(3.6)	1	1	(1.8)	1	1	(1.8)
	Severe	1	1	(1.8)	0	0	(0.0)	1	1	(1.8)
leading to discontinuation		4	3	(5.5)	2	2	(3.6)	2	1	(1.8)

E, Number of adverse events or adverse drug reactions; N, Number of subjects with adverse events or adverse drug reactions; %, Percentage of subjects with adverse events or adverse drug reactions; HDM, house dust mite; AE, adverse event; ADR, adverse drug reaction; JCP, Japanese cedar pollen.

weeks of dual SLIT therapy with ragweed and grass SLIT tablets taken in the morning and evening, respectively; and 2 weeks of dual therapy with the SLIT tablets administered within 5 min of each other. The study results revealed that each treatment regimen was well tolerated. In Japan, two recent studies examined dual SLIT therapy with JCP SLIT drops and SQ HDM SLIT tablets.^{14,15} These studies demonstrated the tolerability of dual SLIT following at least 4-week of monotherapy. Our trial involved 4 weeks of monotherapy with either SQ HDM or JCP SLIT tablets followed by an additional 8 weeks of dual therapy, in Japan, the package inserts for these tablets suggest that the patient should refrain from exercise for 2 h before and after administration, resulting in considerably inconvenience to the patient. Therefore, we considered the need to

shorten this window in the design of the present study. As is standard clinical use in Japan, each tablet was administered at an initial dose for 1 week and increased to a maintenance dose thereafter. Our results demonstrate that concomitant administration of both tablets within 5 min for dual therapy is safe, and we anticipate that treatment adherence may be expected to improve by the short (within 5 min) dosing window.

In our trial, the level of IgE and IgG4 specific *D. farinae*, *D. pteronyssinus*, and JCP significantly increased after treatment. Although the significant change of *D. farinae* specific IgE in the JCP-first group was accidentally observed at week 4, a further obvious increase was subsequently confirmed. The magnitude of the changes induced by treatments were comparable to that detected

Table 3

ADRs reported by 5% or more of subjects in total.

Preferred Term (MedDRA/J v21.1)	HDM-first group						JCP-first group					
	All Period		Period 1		Period 2		All Period		Period 1		Period 2	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Mouth swelling	14	(25.9)	11	(20.4)	6	(11.3)	14	(25.5)	6	(10.9)	12	(21.8)
Oral pruritus	12	(22.2)	11	(20.4)	9	(17.0)	12	(21.8)	7	(12.7)	6	(10.9)
Throat irritation	12	(22.2)	8	(14.8)	7	(13.2)	8	(14.5)	5	(9.1)	6	(10.9)
Rhinorrhoea	11	(20.4)	5	(9.3)	7	(13.2)	6	(10.9)	5	(9.1)	5	(9.1)
Oropharyngeal discomfort	5	(9.3)	4	(7.4)	2	(3.8)	11	(20.0)	3	(5.5)	9	(16.4)
Eye pruritus	5	(9.3)	4	(7.4)	2	(3.8)	7	(12.7)	5	(9.1)	4	(7.3)
Ear pruritus	7	(13.0)	6	(11.1)	3	(5.7)	5	(9.1)	4	(7.3)	3	(5.5)
Laryngeal discomfort	5	(9.3)	2	(3.7)	4	(7.5)	6	(10.9)	1	(1.8)	5	(9.1)
Tongue pruritus	7	(13.0)	6	(11.1)	3	(5.7)	4	(7.3)	2	(3.6)	3	(5.5)
Oropharyngeal pain	7	(13.0)	4	(7.4)	3	(5.7)	3	(5.5)	1	(1.8)	2	(3.6)
Oral discomfort	1	(1.9)	0	(0.0)	1	(1.9)	8	(14.5)	2	(3.6)	7	(12.7)
Paraesthesia oral	2	(3.7)	0	(0.0)	2	(3.8)	5	(9.1)	0	(0.0)	5	(9.1)
Stomatitis	3	(5.6)	3	(5.6)	1	(1.9)	4	(7.3)	2	(3.6)	4	(7.3)
Nasal congestion	4	(7.4)	1	(1.9)	3	(5.7)	3	(5.5)	2	(3.6)	2	(3.6)

ADR, Adverse drug reaction; MedDRA, Medical dictionary of regulatory activities; HDM, house dust mite; JCP, Japanese cedar pollen; N, Number of subjects with adverse drug reaction; %, Percentage of subjects with adverse drug reaction.

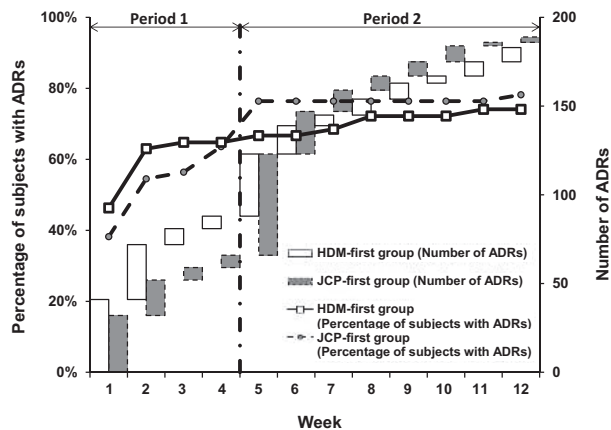


Fig. 3. Percentage of subjects with ADRs (line chart) and running total of ADRs (bar chart) throughout all period. Bar chart indicates weekly and cumulative number of ADRs. ADR, adverse drug reaction; HDM, house dust mite; JCP, Japanese cedar pollen.

in previous trials of SQ HDM SLIT tablet monotherapy⁶ and other immunotherapy regimens.^{18,19} Thus, dual therapy with administration of both SLIT tablets within 5 min appears to induce similar immunological responses to those induced during monotherapy. The European Medicines Agency has noted that mixing multiple allergens may affect drug stability, clinical effectiveness, and safety, and thus recommends that allergens belonging to different “homologous groups” should not be mixed, and that mixtures of allergens with proteolytic activities, such as HDM, should not be used at all.²⁰ Demoly *et al.* reported that separate allergen preparations are preferable when implementing immunotherapy with non-homologous allergens, such as HDM and grass pollen.²¹ The HDM and JCP allergens present in the SLIT tablets used in this trial are non-homologous, and the SQ HDM SLIT tablet includes *Der p1*, which has cysteine protease activity, as a major allergen. Nevertheless, we observed specific immunological responses to both allergens. Even though the SLIT tablets were taken within 5 min of each other, and some residual HDM cysteine protease activity could have remained in the oral cavity before JCP SLIT tablet administration, it is unlikely to have affected the trial results.

This trial has some limitations. The aim of the trial was to investigate the safety and immunological response of monotherapy followed by dual therapy with SQ HDM and JCP SLIT tablets, and we did not measure efficacy and record the safety profile and immunological response for longer than 8 weeks of dual therapy. Because allergen immunotherapy is recommended over a period of 3–5 years,²² we expect to obtain further information on the long-term efficacy, and safety profile and immunological response of dual therapy with SQ HDM and JCP SLIT tablets during future clinical use.

In conclusion, this trial tested dual allergen SLIT tablet therapy in Japanese patients with coexisting HDM and JCP allergic rhinitis for 4 weeks of monotherapy followed by 8 weeks of dual therapy in which the two SLIT tablets were taken within 5 min of each other. Regardless of which allergen tablet was administered during monotherapy, dual SLIT therapy was well tolerated and the safety profile did not differ substantially from those observed in previous studies of monotherapy with each SLIT tablet. We also confirmed that dual SLIT therapy induced an immunological response to HDM and JCP allergens comparable to that seen during monotherapy with either SLIT tablet alone.

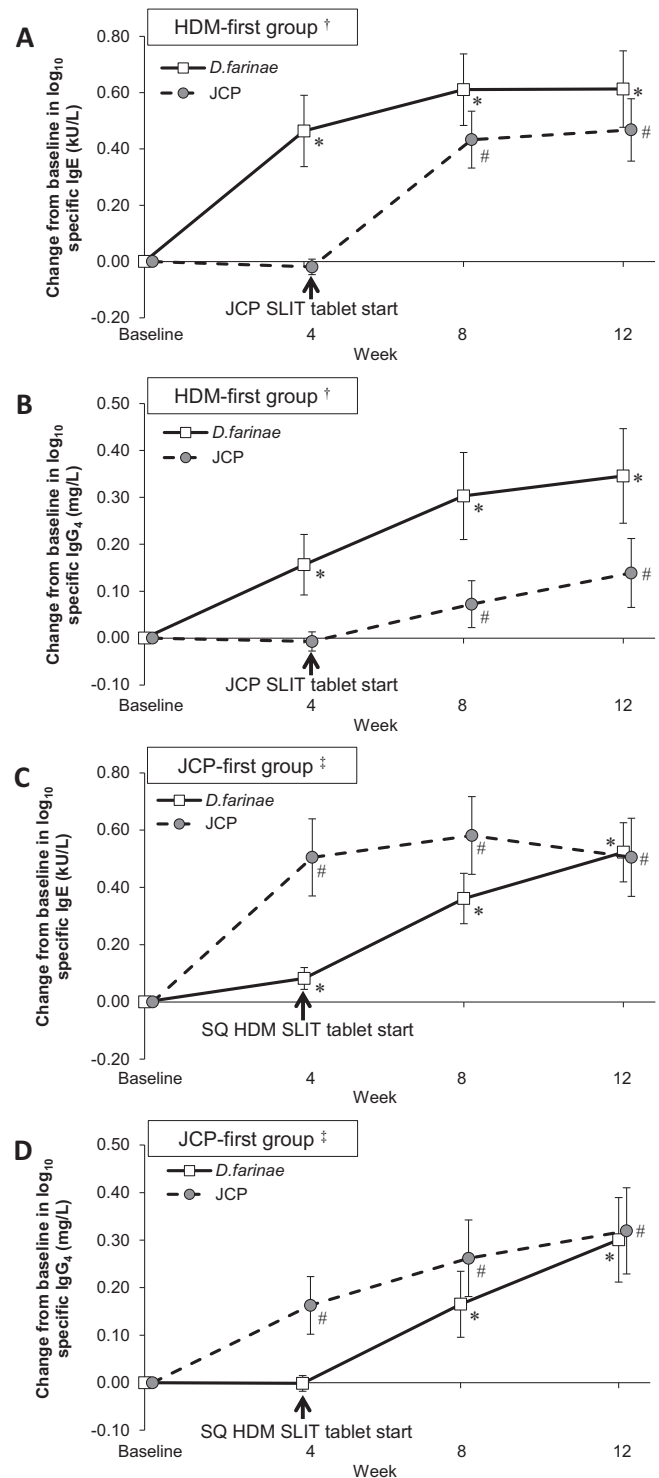


Fig. 4. Means with 95% CIs of immunologic parameters in the change from baseline levels of *D. farinae* and JCP IgE in HDM-first group (A), *D. farinae* and JCP IgG4 in HDM-first group (B), *D. farinae* and JCP IgE in JCP-first group (C), *D. farinae* IgG4 and JCP IgG4 in JCP-first group (D) throughout the all period. Means and CIs were calculated using the log10-transformed data. *Statistically significant difference from baseline in *D. farinae*. #Statistically significant difference from baseline in JCP. CI, confidence interval; *D. farinae*, *Dermatophagoides farinae*; JCP, Japanese cedar pollen; kU/L, kilo-units per liter; HDM, house dust mite. [†]N = 33 at baseline. [‡]N = 42 at baseline.

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Conflict of interest

MG has received honoraria from Torii, Taiho, Mitsubishi Tanabe, Hisamitsu, and research funding from All Japan Coffee Association. KO has received honoraria from Torii, Taiho, Mitsubishi Tanabe, and writing fee from Torii. AY has received honoraria from Torii, and writing fee from Torii, and research funding from Torii. KK has received honoraria from Torii. SU has received research funding from Torii. SF has received honoraria from Torii and research funding from Torii. HS has received honoraria from Torii, Sanofi. MO has received honoraria from Mitsubishi Tanabe, and others from ALK-Abelló. TM has received research funding from Torii. KM has received honoraria from Torii, MSD, Sanofi, Taiho and Kyorin. YOK has received honoraria from Torii, Shionogi, Kyorin, Taiho, Mitsubishi Tanabe, and research funding from Kyorin, Yamada Bee Farm. SK, HH, NH and HT are employed by Torii. The rest of author has no conflict of interest.

Authors' contributions

MG and KO designed this trial. MG, AY, YOG, HN, SU, TU, KK, MY, SF, MS, HS, NI, EM, TE, NO, HK, MO, MA, MT, TT, YI, SY, TM, KM, YOK, investigators, contributed to the conduct of the study and data collection and interpretation. SK, HH, NH, HT participated in the discussion of trial design, conducted the trial, and interpreted the collected data. All authors gave approval on the submission of the manuscript.

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