

Long-Term Efficacy and Dose-Finding Trial of Japanese Cedar Pollen Sublingual Immunotherapy Tablet



Minoru Gotoh, MD, PhD^a, Syuji Yonekura, MD, PhD^b, Toru Imai, MD, PhD^c, Shinya Kaneko, MSc^d, Eiji Horikawa, BSc^d, Akiyoshi Konno, MD, PhD^e, Yoshitaka Okamoto, MD, PhD^b, and Kimihiro Okubo, MD, PhD^a Tokyo, Chiba, and Fukushima, Japan

What is already known about this topic? The long-term efficacy of sublingual immunotherapy (SLIT) tablet in patients with seasonal allergic rhinitis was proven in several double-blind, placebo-controlled clinical trials using single or multiple active arms without confirming dose dependency.

What does this article add to our knowledge? This trial provides the first evidence of SLIT tablet efficacy depending on the treatment duration, with an optimal dose determined by statistically significant differences among active doses in the first year of a 5-year double-blind, placebo-controlled trial.

How does this study impact current management guidelines? The optimal dose of SLIT tablet determined by dose dependency should be considered to gain the maximum continuous improvement in rhinoconjunctivitis symptoms and frequency of pharmacotherapy during the long-term treatment period.

BACKGROUND: Japanese cedar (JC) pollinosis is a common allergic rhinitis in Japan. The JC pollen sublingual immunotherapy (SLIT) tablet was developed using the highest concentration of JC pollen extract.

OBJECTIVE: This was a randomized, double-blind, placebo-controlled phase II/III trial to investigate the optimal dose of the JC pollen SLIT tablet and examine long-term efficacy and safety for 3 years with the selected dose, and 2-year follow-up.

METHODS: A total of 1042 patients with JC pollinosis (aged 5–64 years) were equally randomized into 4 groups and received daily treatment with 2,000, 5,000, or 10,000 Japanese allergy unit (JAU) or placebo. The primary end point was the total nasal symptom and medication score (TNSMS) during the peak

symptom period in the first season. Key secondary end points were TNSMS for the JC pollen dispersion season and total nasal and ocular symptom and medication score for the peak symptom period and JC pollen dispersion season.

RESULTS: For the primary end point, absolute reductions and relative mean reductions in TNSMS compared with placebo were 1.50 and 21.4%, 2.24 and 32.1%, and 2.18 and 31.2% for 2,000, 5,000, and 10,000 JAU, respectively ($P < .001$ in all groups). For all key secondary end points, efficacy was confirmed for all doses ($P < .001$ in all groups). The treatment was well tolerated. Long-term efficacy of 5,000 JAU was shown over the 3 years.

CONCLUSIONS: The optimal dose of the JC pollen SLIT tablet was 5,000 JAU, with good efficacy and safety over a 3-year

^aDepartment of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

^bDepartment of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

^cAssociation of Pollen Information of Japan, Tokyo, Japan

^dDepartment of Clinical Development, Torii Pharmaceutical Co., Ltd, Tokyo, Japan

^eAllergy and Head and Neck Tumor Center, Southern Tohoku General Hospital, Fukushima, Japan

The trial was sponsored by Torii, Tokyo, Japan, who assumes overall responsibility for the trial and was involved in both the trial design and conduct.

Conflicts of interest: M. Gotoh has received lecture fees from Torii, Taiho, Kyorin, and Sanofi S.A.; and has served on speakers bureaus for Torii and Taiho. S. Yonekura has received lecture fees from Torii. T. Imai has received consultancy fees from Torii. S. Kaneko and E. Horikawa are employed by Torii. A. Konno has received consultancy fees from Torii. Y. Okamoto has received consultancy fees from Torii; has received grants from Torii, Shionogi, Yamada Bee Farm, Yakult Honsha, Kyowa Hakko Kirin, Kyorin, Taiho, and Mitsubishi Tanabe; has received

lecture fees from Torii, Shionogi, Kyowa Hakko Kirin, Kyorin, Taiho, Mitsubishi Tanabe, GlaxoSmithKline, MSD, Sanofi, Thermo Fisher Scientific, Taiho Toyama, Nippon Zoki, and Otsuka. K. Okubo has received consultancy fees from Torii, Kyowa Hakko Kirin, Teikoku, Hisamitsu, Ono, Taiho, Astellas, and Mitsubishi Tanabe; and has received lecture fees from Sanofi, Shionogi, Kyorin, and Meiji.

Received for publication June 21, 2018; revised October 17, 2018; accepted for publication November 26, 2018.

Available online December 8, 2018.

Corresponding author: Minoru Gotoh, MD, PhD, Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail: m.gotoh@nms.ac.jp. 2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.11.044>

Abbreviations used

AA group- active-to-active, 5,000 JAU to 5,000 JAU, group
 AE- Adverse event
 AIT- Allergen immunotherapy
 AP group- active-to-placebo, 5,000 JAU to placebo, group
 AR- Allergic rhinitis
 IMP- Investigational medicinal product
 JAU- Japanese allergy unit
 JC- Japanese cedar
 JRQLQ- Japanese Rhinoconjunctivitis Quality of Life
 Questionnaire
 PA group- placebo-to-active, placebo to 5,000 JAU, group
 PP group- placebo-to-placebo group
 SLIT- Sublingual immunotherapy
 TNSMS- Total nasal symptom and medication score

treatment period. This sustained effect was dependent on treatment duration. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1287-97)

Key words: Allergy immunotherapy; Sublingual immunotherapy; Japanese cedar; Allergy; Allergic rhinitis; Conjunctivitis; Children

INTRODUCTION

Japanese cedar (JC) pollinosis is the most common seasonal allergic rhinitis (AR) in Japan and is caused by JC pollen.¹⁻⁴ In Tokyo, JC pollen usually begins to disperse in mid-February and continues through late April. Because people are exposed to JC pollen for approximately 10 weeks, their quality of life and work productivity are greatly impacted. The prevalence of JC pollinosis is estimated to exceed 1 in 4 people (30 million) throughout Japan and is referred to as a “national disease.”

Unlike allergy pharmacotherapy, allergen immunotherapy (AIT) is recognized as the only treatment option that can alter the natural course of allergic disease.⁵⁻¹¹ Japanese guidelines for AR treatment¹² recommend AIT for seasonal and perennial AR of all severities. Currently, it is possible to use sublingual immunotherapy (SLIT) extracts for JC pollinosis. However, the extracts cannot be manufactured in high concentrations because of technical issues.

The JC pollen SLIT tablet is a rapidly soluble, lyophilized preparation at a high concentration that is not possible to manufacture in the form of JC pollen SLIT extracts. A large, double-blind, placebo-controlled clinical field trial was conducted during a first JC pollen dispersion season to determine the optimal dose among 3 active doses of the SLIT tablet in Japanese patients (aged 5-64 years) with JC pollinosis. After determining the optimal dose, both placebo and optimal-dose groups continued the trial to investigate long-term efficacy and safety, up to a third JC pollen dispersion season. Subsequently, the trial requires additional evaluation for 2 years without the investigational medicinal product (IMP) treatment to investigate disease modification effect. Herein, we report the results through the third JC pollen dispersion season of the trial.

METHODS**Clinical trial design**

This randomized, parallel-group, double-blind, placebo-controlled trial was begun in July 2014 (JapicCTI no. 142579).

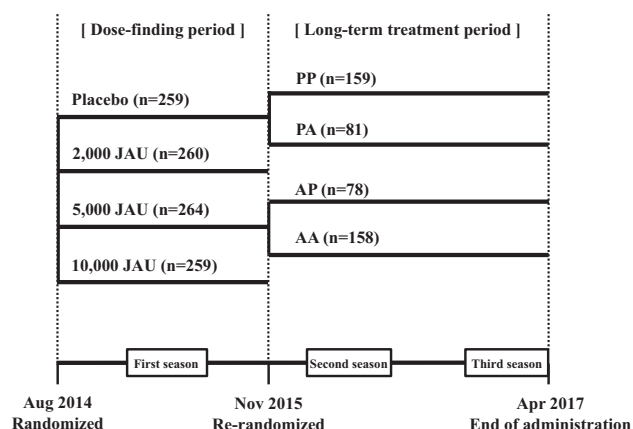


FIGURE 1. Trial design. Mean treatment periods before the start of the JC pollen dispersion season were as follows: First season: 6 months in all groups; Second season: 18 months in PP and AA groups, 15 months of Placebo + 3 months of Active in the PA group, 15 months of Active + 3 months of Placebo in the AP group; Third season: 30 months in PP and AA groups, 15 months of Placebo + 15 months of Active in the PA group, 15 months of Active + 15 months of Placebo in the AP group.

This trial included a dose-finding period, a long-term treatment period, and an observational period. In this study, we report the data collected up to the long-term administration period (Figure 1). A total of 1042 participants from 41 sites in Tokyo and surrounding areas were randomly assigned at a ratio of 1:1:1:1 to the following 4 groups: JC pollen SLIT tablet of 2,000 Japanese allergy unit (JAU), 5,000 JAU, or 10,000 JAU, or the placebo group. Bell Medical Solutions Inc (Tokyo, Japan) was responsible for the group assignment. Participants assigned to the 5,000 JAU group took a 5,000 JAU JC pollen SLIT tablet every day, after taking a 2,000 JAU tablet every day for 1 week. Participants assigned to the 10,000 JAU group took a 10,000 JAU JC pollen SLIT tablet every day after taking 2,000 JAU and 5,000 JAU tablets for 1 week each. During up dosing, patients were provided with weekly packages of IMP to maintain blinding. After determining the optimal dose on the basis of results of the dose-finding period, participants assigned to the optimal dose and placebo groups were transitioned to the long-term treatment period whereas all participants in the other 2 active groups had to discontinue the trial. Fifteen months after the first administration (which was just 3 months before the second season), the transitioned participants were randomly reassigned at a ratio of 2:1 to a group that continued to receive the same doses (active-to-active, 5,000 JAU to 5,000 JAU, group [AA group]; placebo-to-placebo group [PP group]) or a group that was switched to other doses (active-to-placebo, 5,000 JAU to placebo, group [AP group]; placebo-to-active, placebo to 5,000 JAU, group [PA group]). All participants were required to follow the 2-step up dosing regimen again at the beginning of the long-term treatment period, to maintain blinding, with weekly IMP packages. The participants in the AA and PP groups were eventually treated with the same doses for approximately 30 months at the beginning of the third season, whereas the participants in the AP and PA groups received active and placebo treatment for approximately 15 months each.

The institutional review boards at all sites approved this trial, which was performed in accordance with the Declaration of Helsinki

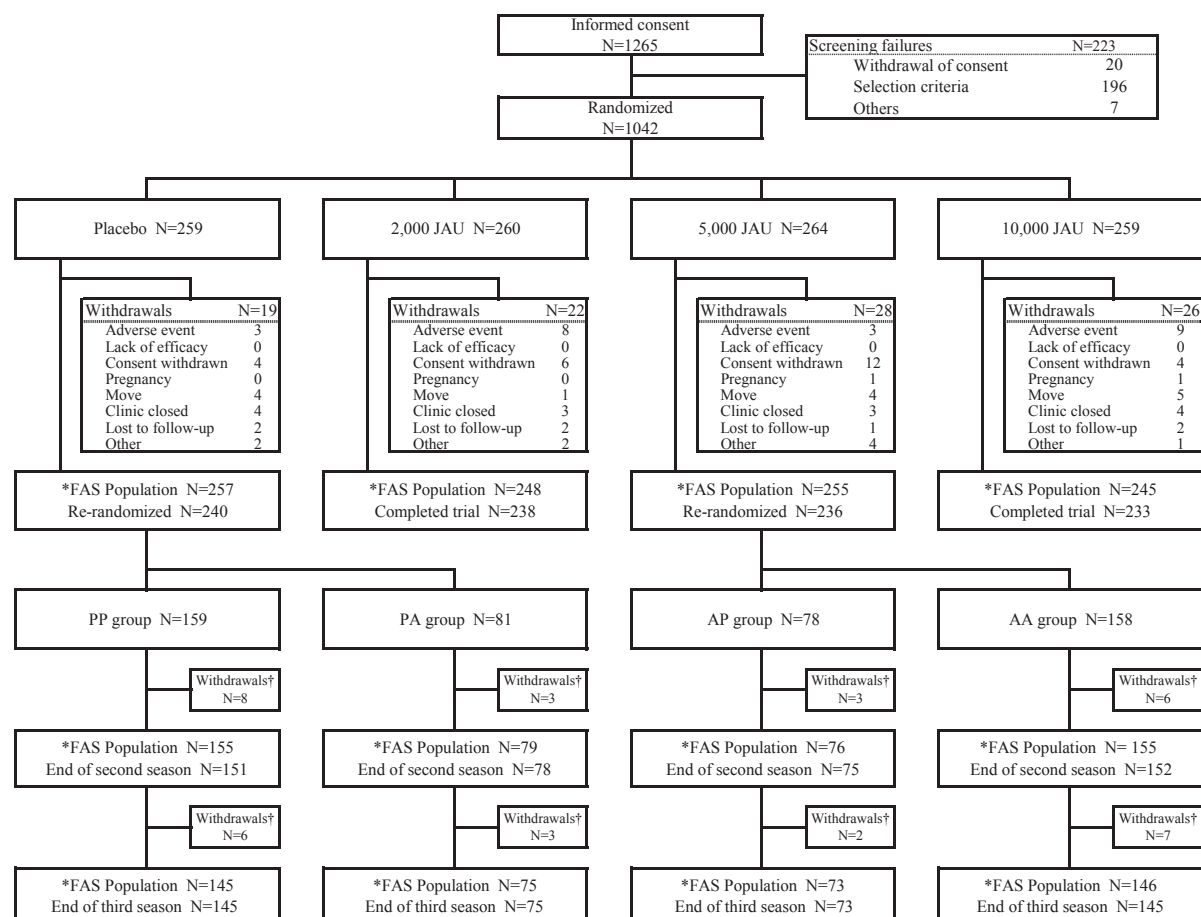


FIGURE 2. Participant disposition. *The primary analysis set was the full analysis set (FAS), which included participants who entered at least once information regarding symptom scores and medication use into the electronic diary during the peak symptom period. †To maintain blinding, evaluated on all data during long-term treatment period: 10 participants, AEs; 1 participant, lack of efficacy; 13 participants, consent withdrawn; 2 participants, pregnancy; 8 participants, move; 2 participants, lost to follow-up; 2 participants, other reasons.

and the guidelines for Good Clinical Practice. All patients provided their written informed consent for participation in the trial. In the case of minor-aged patients, consent was obtained from a legal representative.

Participants

Study participants were patients with JC pollinosis who fulfilled the inclusion criteria as follows: male or female, aged 5 to 64 years, 3.5 UA/mL or more of JC pollen-specific IgE antibody, at least 1 of 3 symptoms (sneezing, runny nose, and blocked nose) persisting for at least 1 week with 2+ or more severity as evaluated by the Japanese guideline for AR treatment during the JC pollen dispersion season in the previous consecutive 2 years. The following participants were excluded: those with 50 UA/mL or more of specific IgE against any of the following allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat dander, dog dander, Japanese cypress, orchard grass, and Japanese alder; those who had perennial AR requiring treatment; those who had previously undergone JC pollinosis-specific immunotherapy; and those who had experienced a bronchial asthma attack within the past 5 years.

Investigational medicinal product

The JC pollen SLIT tablet was manufactured and supplied by ALK-Abelló (Hørsholm, Denmark) using the same technology as that used for ALK's fast-dissolving freeze-dried SLIT tablet.¹³ In this trial, a placebo or the JC pollen SLIT tablet in doses of 2,000, 5,000, and 10,000 JAU was used. JAU is a unique titer unit based on standardized allergen extract, developed by the Japanese Society of Allergology.¹⁴ Participants took 1 tablet daily under the tongue for 1 minute and then swallowed. The first administration was performed at each site, and participants were monitored by physicians for at least 30 minutes in the interest of safety. The placebo tablet was similar to the active intervention medication with regard to appearance, smell, and taste.

Outcome measures

The JC pollen count was measured in central Tokyo using a Durham sampler. Three nasal symptoms (sneezing, runny nose, and blocked nose) were each evaluated on a scale of 0 to 4 points, and 2 conjunctivitis symptoms (eye itchiness and watery eyes) were each evaluated on a scale of 0 to 3 points.^{12,15} To treat intolerable symptoms of rhinitis or conjunctivitis, rescue medications (ie,

TABLE I. Baseline characteristics and demography in the dose-finding period (A) and the long-term treatment period (B)

A.					
Treatment group	Placebo (N = 259)	2,000 JAU (N = 260)	5,000 JAU (N = 264)	10,000 JAU (N = 259)	Overall (N = 1042)
Sex, n (%)					
Male	110 (42.5)	108 (41.5)	120 (45.5)	113 (43.6)	451 (43.3)
Female	149 (57.5)	152 (58.5)	144 (54.5)	146 (56.4)	591 (56.7)
Age (y), mean $\pm$ SD	34.6 $\pm$ 14.7	34.8 $\pm$ 15.1	34.5 $\pm$ 15.0	35.6 $\pm$ 15.4	34.9 $\pm$ 15.0
Years with JC pollinosis, mean $\pm$ SD	15.0 $\pm$ 9.2	15.9 $\pm$ 9.4	16.1 $\pm$ 9.5	16.1 $\pm$ 9.6	15.8 $\pm$ 9.4
JC pollen-specific IgE (UA/mL), n (%)					
≥ 3.5 -<17.5	129 (49.8)	104 (40.0)	123 (46.6)	114 (44.0)	470 (45.1)
≥ 17.5 -<50	84 (32.4)	92 (35.4)	95 (36.0)	85 (32.8)	356 (34.2)
≥ 50 -<100	35 (13.5)	41 (15.8)	33 (12.5)	40 (15.4)	149 (14.3)
≥ 100	11 (4.2)	23 (8.8)	13 (4.9)	20 (7.7)	67 (6.4)
Sensitization status, n (%)					
Monosensitized	34 (13.1)	37 (14.2)	28 (10.6)	29 (11.2)	128 (12.3)

B.					
Treatment group	PP group (N = 159)	AP group (N = 78)	PA group (N = 81)	AA group (N = 158)	Total (N = 476)
Sex, n (%)					
Male	71 (44.7)	41 (52.6)	30 (37.0)	69 (43.7)	211 (44.3)
Female	88 (55.3)	37 (47.4)	51 (63.0)	89 (56.3)	265 (55.7)
Age (y), mean $\pm$ SD	35.0 $\pm$ 14.4	35.6 $\pm$ 14.8	33.8 $\pm$ 14.8	34.3 $\pm$ 15.2	34.7 $\pm$ 14.8
Years with JC pollinosis, mean $\pm$ SD	15.2 $\pm$ 9.0	16.4 $\pm$ 9.7	14.8 $\pm$ 9.5	16.6 $\pm$ 9.2	15.8 $\pm$ 9.3
JC pollen-specific IgE (UA/mL), n (%)					
≥ 3.5 -<17.5	76 (47.8)	43 (55.1)	42 (51.9)	63 (39.9)	224 (47.1)
≥ 17.5 -<50	55 (34.6)	26 (33.3)	25 (30.9)	61 (38.6)	167 (35.1)
≥ 50 -<100	22 (13.8)	8 (10.3)	11 (13.6)	23 (14.6)	64 (13.4)
≥ 100	6 (3.8)	1 (1.3)	3 (3.7)	11 (7.0)	21 (4.4)
Sensitization status, n (%)					
Monosensitized	20 (12.6)	11 (14.1)	8 (9.9)	13 (8.2)	52 (10.9)

The subjects belonging to the optimal-dose (5000 JAU group) and placebo groups during the dose-finding period were reassigned during the long-term treatment period to the following 4 groups at a ratio of 2:1:1:2: AA, AP, PA, and PP.

antihistamine tablets and eye drops or nasal vasoconstrictors) were provided by the trial sponsor. Children who were unable to swallow tablets could opt for a dry syrup preparation. Rescue medication use was permitted only when participants felt their symptoms to be intolerable; prophylactic administration was prohibited. To standardize the rescue medication use, the above-mentioned rescue medication can be used in the event of the following intolerable symptoms: blocked nose that can be treated with tramazoline hydrochloride and ocular symptoms (itchy or watery eyes) that can be treated with ketotifen fumarate. Fexofenadine hydrochloride use was permitted if these intolerable symptoms persisted despite the use of the medications or in the presence of other intolerable symptoms, such as sneezing and runny nose. The score for each rescue medication was calculated on the basis of its use or nonuse (3 points or 0 point, respectively). Evaluation was performed during each JC pollen dispersion season and peak symptom period. The JC pollen dispersion season was defined as starting on the first day of the first 2 consecutive days after January 1 on which there was a pollen count of over 1 grain/cm²/d, and ending on the day before the first of 3 consecutive days on which there was a pollen count of 0 grain/cm²/d. The peak symptom period was composed of 3 weeks and defined as the week with the worst symptoms, based on the sum of nasal symptoms and

medication score for all participants, plus the week before and after that week. However, Japanese cypress pollen dispersion season generally starts at the beginning of April; thus, to prevent confounding owing to allergic symptoms caused by Japanese cypress pollen, March 31 was defined as the end of the peak symptom period. The primary end point was the total nasal symptom and medication score (TNSMS) during the peak symptom period. Key secondary end points were TNSMS for the JC pollen season and the total nasal and ocular symptom and medication score for the peak symptom period and JC pollen dispersion season. Details on the scoring scale can be viewed in [Tables E1, E2, and E3](#) in this article's Online Repository at www.jaci-inpractice.org. Scores for each symptom and medication were recorded each year from January 8 to April 30 and were entered in an electronic diary every day by participants. A well-day was defined as a day when all symptoms were scored 0 or 1 and there was no rescue medication use. A severe-symptom day was a day when at least 1 symptom was evaluated with the highest score.

The participants completed the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ)^{12,16} twice (in the middle and end of March) each year. Adverse events (AEs) that occurred after initiating IMP administration were noted and evaluated as safety information.

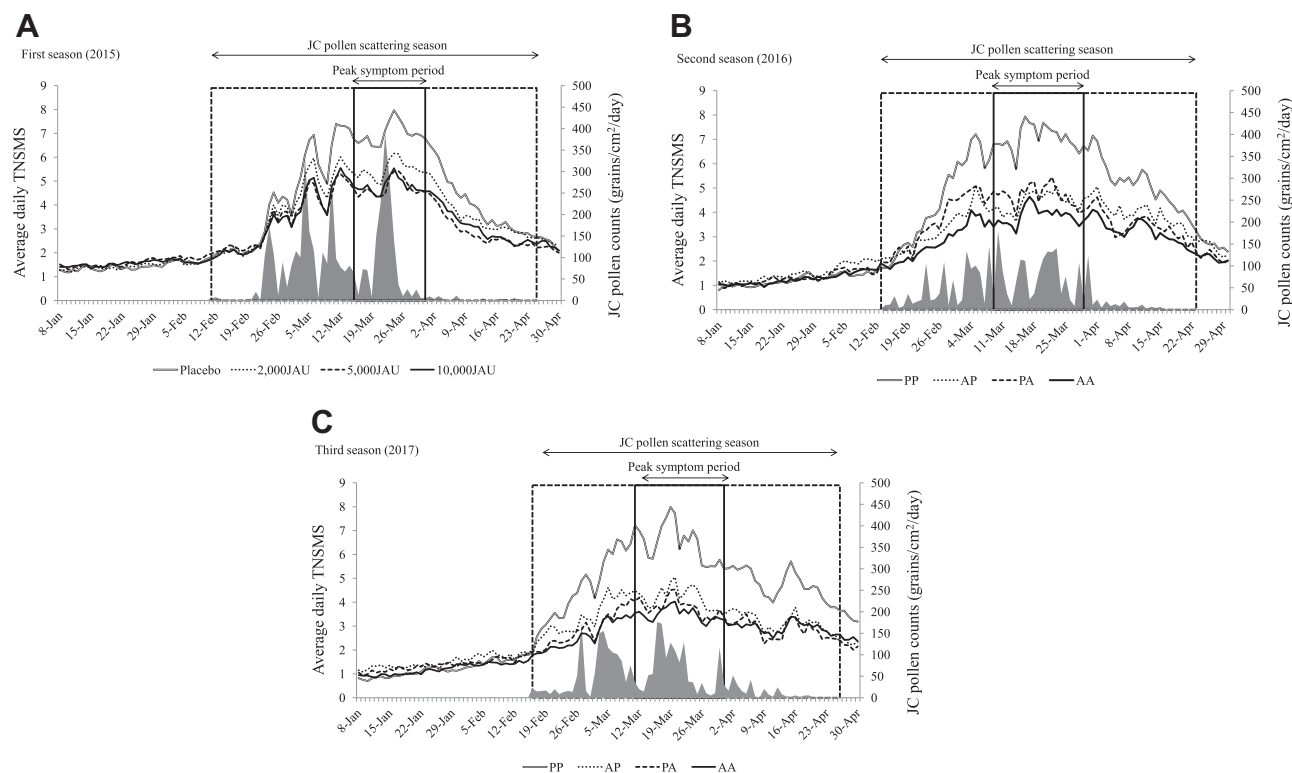


FIGURE 3. Daily averaged TNSMS in the first (A), second (B), and third (C) seasons. JC pollen counts shown with gray shading.

Statistical analysis

The sample size during the dose-finding period was based on previously reported results of TNSMS in the first season of JC pollen SLIT extracts¹⁵ and was calculated using the relative difference between the mean values of the placebo and lowest-dose groups (2,000 JAU group) to be -18% .

Hypothesizing the mean relative difference of TNSMS in the 2,000 JAU group (lowest-dose group), 5,000 JAU group, and 10,000 JAU group to be -18% , -20% , and -22% , respectively, in the primary outcome measure, a test was performed using the closed testing procedure from the highest dose. The number of cases wherein the difference between the placebo and 2,000 JAU (lowest-dose) groups could be detected at a probability of greater than or equal to 80% was 200 cases per group. Considering the possible number of dropouts, 230 cases per group was set as the sample size. The sample size for the long-term treatment period was the total number of participants in the groups receiving the optimal dose and placebo who completed the dose-finding period, without implementing statistical sample size calculation.

In primary analysis, we applied a linear model with treatment groups as explanatory variables. The primary evaluation set was the full analysis set (FAS) and included participants whose TNSMS during the peak symptom period had been measured at least once. A closed testing procedure, in which tests were performed sequentially from a high dose, was used to adjust for multiplicity in the primary analysis. The analysis during the long-term treatment period involved the same analyses as those performed during the dose-finding period, with each dose group from the dose-finding period being reassigned to 4 new groups (PP, PA, AP, and AA groups). The aim of this study was to conduct an exploratory investigation in the analyses of the second and subsequent seasons. Accordingly, the results were not adjusted for

multiplicity. Analyses in the second and subsequent seasons were conducted by a third party to ensure that the trial could be continued while maintaining its blindness. Details on statistical analyses are available in the [Methods](#) section and [Tables E4](#) and [E5](#) in this article's Online Repository at www.jaci-inpractice.org.

RESULTS

Participants and JC pollen counts

The disposition of study participants is shown in [Figure 2](#). No intergroup differences were observed in the number of discontinuations or reasons for discontinuation. The 5,000 JAU (optimal dose, $N = 236$) and placebo ($N = 240$) groups transitioned to the long-term treatment period and were randomly reassigned to the AA ($N = 158$), AP ($N = 78$), PA ($N = 81$), or PP ($N = 159$) groups. The trial is currently ongoing under blinded conditions.

Participant characteristics in the dose-finding and long-term treatment periods are presented in [Table I](#). No major differences were observed between groups based on participant characteristics.

There were no large differences in the JC pollen counts among the seasons for both peak symptom periods and JC pollen dispersion seasons. Details on the JC pollen counts and evaluation period are available in the Results section and [Table E6](#) in this article's Online Repository at www.jaci-inpractice.org.

Efficacy and safety during the dose-finding period (first season)

Evaluation in the dose-finding period was performed during the 2015 JC pollen dispersion season. Daily averaged TNSMS during the period is presented in [Figure 3, A](#). The mean TNSMS

TABLE II. Analytical results for the primary end point (TNSMS) and key secondary end point (TNOSMS) in the peak symptom period and JC pollen dispersion season (FAS)

Evaluation period	Treatment group	N	LS mean	Absolute difference from placebo (95% CI) Relative difference to placebo (95% CI)	P value	Absolute difference from 2,000 JAU (95% CI) Relative difference to 2,000 JAU (95% CI)	P value	Absolute difference from 5,000 JAU (95% CI) Relative difference to 5,000 JAU (95% CI)	P value
TNSMS (Linear)									
Peak symptom period	Placebo	257	6.98	—	—	—	—	—	—
	2,000 JAU	248	5.49	1.50 (0.90 to 2.09) 21.4% (13.5% to 28.8%)	<.001	—	—	—	—
	5,000 JAU	255	4.74	2.24 (1.65 to 2.83) 32.1% (24.6% to 39.1%)	<.001	0.74 (0.15 to 1.34) 13.6% (2.9% to 23.2%)	.014	—	—
	10,000 JAU	245	4.80	2.18 (1.58 to 2.77) 31.2% (23.6% to 38.3%)	<.001	0.68 (0.08 to 1.28) 12.5% (1.6% to 22.3%)	.026	−0.06 (−0.66 to 0.54) −1.3% (−14.8% to 10.7%)	.843
JC pollen dispersion season	Placebo	257	4.74	—	—	—	—	—	—
	2,000 JAU	248	4.01	0.73 (0.33 to 1.13) 15.4% (7.2% to 23.0%)	<.001	—	—	—	—
	5,000 JAU	255	3.53	1.21 (0.81 to 1.61) 25.5% (17.7% to 32.7%)	<.001	0.48 (0.07 to 0.88) 11.9% (1.9% to 21.0%)	.021	—	—
	10,000 JAU	245	3.57	1.16 (0.76 to 1.57) 24.6% (16.7% to 31.9%)	<.001	0.43 (0.02 to 0.84) 10.8% (0.7% to 20.1%)	.038	−0.04 (−0.45 to 0.36) −1.3% (−13.6% to 9.7%)	.830
TNOSMS (Linear)									
Peak symptom period	Placebo	257	9.66	—	—	—	—	—	—
	2,000 JAU	248	7.26	2.40 (1.58 to 3.23) 24.9% (17.0% to 32.2%)	<.001	—	—	—	—
	5,000 JAU	255	6.31	3.35 (2.53 to 4.17) 34.7% (27.2% to 41.6%)	<.001	0.95 (0.12 to 1.77) 13.0% (1.8% to 23.1%)	.025	—	—
	10,000 JAU	245	6.32	3.34 (2.51 to 4.17) 34.6% (27.1% to 41.6%)	<.001	0.94 (0.10 to 1.77) 12.9% (1.5% to 23.1%)	.028	−0.01 (−0.84 to 0.82) −0.1% (−14.2% to 12.2%)	.984
JC pollen dispersion season	Placebo	257	6.41	—	—	—	—	—	—
	2,000 JAU	248	5.24	1.17 (0.62 to 1.72) 18.2% (10.0% to 25.8%)	<.001	—	—	—	—
	5,000 JAU	255	4.61	1.80 (1.25 to 2.35) 28.1% (20.3% to 35.3%)	<.001	0.63 (0.08 to 1.18) 12.0% (1.5% to 21.5%)	.026	—	—
	10,000 JAU	245	4.61	1.80 (1.25 to 2.36) 28.1% (20.3% to 35.4%)	<.001	0.63 (0.07 to 1.19) 12.1% (1.5% to 21.7%)	.027	0.00 (−0.55 to 0.56) 0.1% (−12.7% to 11.5%)	.990

FAS, Full analysis set; LS, least squares; TNOSMS, total nasal and ocular symptom and medication score.

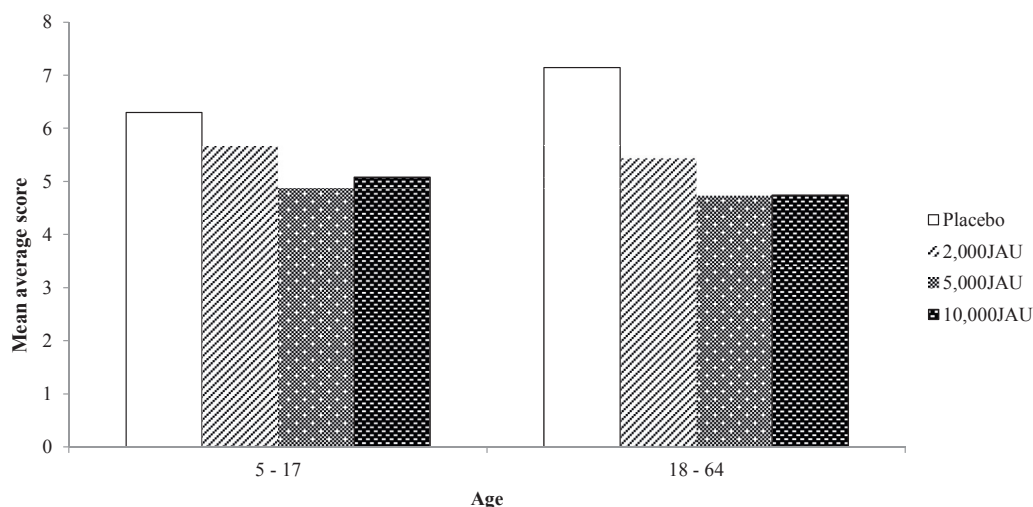


FIGURE 4. Comparison of least square means of TNSMS during the peak symptom period of the dose-finding period between children (aged 5-17 years) and adults (aged 18-64 years).

TABLE III. Summary of safety (dose-finding period)

Classifications of AEs	Placebo (N = 259)		2,000 JAU (N = 260)		5,000 JAU (N = 264)		10,000 JAU (N = 259)		Active all (N = 783)		Overall (N = 1042)	
	n	%	n	%	n	%	n	%	n	%	n	%
SAE	5	1.9	6	2.3	5	1.9	3	1.2	14	1.8	19	1.8
IMP-related SAE	—	—	—	—	—	—	—	—	—	—	—	—
AE	200	77.2	220	84.6	219	83.0	212	81.9	651	83.1	851	81.7
Mild	198	76.4	217	83.5	218	82.6	211	81.5	646	82.5	844	81.0
Moderate	13	5.0	21	8.1	16	6.1	15	5.8	52	6.6	65	6.2
Severe	1	0.4	—	—	—	—	—	—	—	—	1	0.1
IMP-related AE	50	19.3	129	49.6	123	46.6	142	54.8	394	50.3	444	42.6
Mild	50	19.3	128	49.2	122	46.2	142	54.8	392	50.1	442	42.4
Moderate	—	—	3	1.2	1	0.4	3	1.2	7	0.9	7	0.7
Severe	—	—	—	—	—	—	—	—	—	—	—	—
WAO systemic AEs	67	25.9	56	21.5	59	22.3	60	23.2	175	22.3	242	23.2
Grade 1	57	22.0	49	18.8	53	20.1	54	20.8	156	19.9	213	20.4
Grade 2	9	3.5	6	2.3	5	1.9	7	2.7	18	2.3	27	2.6
Grade 3	4	1.5	7	2.7	3	1.1	2	0.8	12	1.5	15	1.4
Grade 4	—	—	—	—	—	—	—	—	—	—	—	—
Grade 5	—	—	—	—	—	—	—	—	—	—	—	—
WAO local AEs	46	17.8	120	46.2	127	48.1	142	54.8	389	49.7	435	41.7
Grade 1	33	12.7	112	43.1	110	41.7	128	49.4	350	44.7	383	36.8
Grade 2	20	7.7	16	6.2	28	10.6	22	8.5	66	8.4	87	8.3
Grade 3	1	0.4	—	—	1	0.4	3	1.2	4	0.5	5	0.5

SAE, Serious adverse event; WAO, World Allergy Organization.

of all groups fluctuated in conjunction with the JC pollen situation. Mean scores of the 3 active groups were lower than those of the placebo group. The results for analyses of efficacy during the dose-finding period are presented in Table II. The absolute and relative differences between the adjusted means of TNSMS for the peak symptom period (ie, primary end point) and that in the placebo group were 1.50 and 21.4% in the 2,000 JAU group, 2.24 and 32.1% in the 5,000 JAU group, and 2.18 and 31.2%

in the 10,000 JAU group (all $P < .001$). The least squares mean of TNSMS in the 5,000 JAU group was significantly lower than that in the 2,000 JAU group but was not significantly different from that in the 10,000 JAU group. These results are supported by a linear model analysis of a per-protocol set, a covariate-adjusted analysis of FAS, and a nonparametric analysis. Details on the sensitivity analyses are presented in the Results section and Table E7 in this article's Online Repository

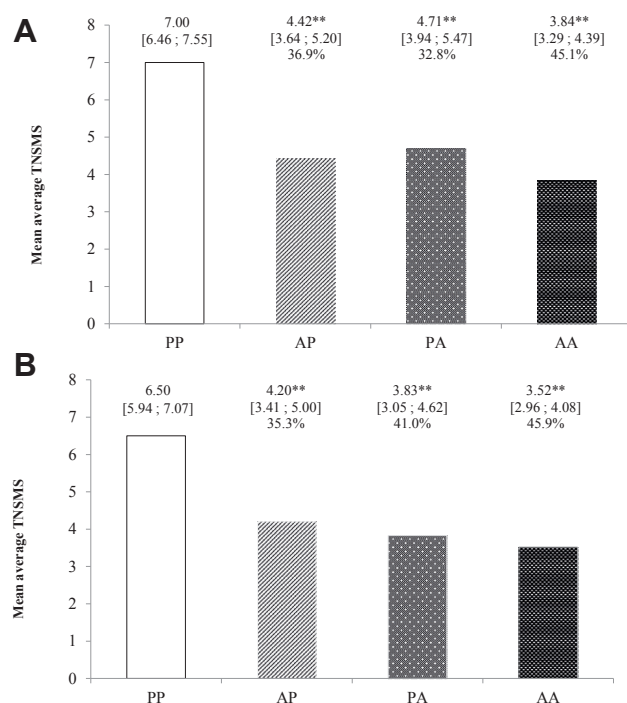


FIGURE 5. Least squares mean of TNSMS with 95% CI and relative difference (%) to the PP group in the peak symptom period of second (A) and third (B) seasons. ** $P < .001$ vs the placebo group.

at www.jaci-inpractice.org. Similarly, the total nasal and ocular symptom and medication score in the same period was significantly lower in each active group than in the placebo group (all $P < .001$). TNSMS of the 2,000 JAU, 5,000 JAU, and 10,000 JAU groups during the peak symptom period among children (aged 5-17 years) was lower than that of the placebo group. Furthermore, TNSMS of the 5,000 JAU and 10,000 JAU groups was lower than that of the 2,000 JAU group, whereas that of the 5,000 JAU and 10,000 JAU groups was equal (Figure 4). In addition, TNSMS of the elderly patients with prolonged histories of JC pollinosis (aged 50-64 years; mean disease duration, 23.1 years) during the peak symptom period in the placebo, 2,000 JAU, 5,000 JAU, and 10,000 JAU groups was 6.67, 4.37, 4.77, and 4.67, respectively. JRQLQ scores in 3 active groups were significantly improved compared with the score of the placebo group (all $P < .001$). Details on the results of general state according to the JRQLQ are presented in the Results section and Figure E1, A, in this article's Online Repository at www.jaci-inpractice.org.

A summary of safety during the dose-finding period is presented in Table III. No deaths or systemic allergic reactions requiring administration of epinephrine occurred. Serious AEs occurred at an equivalent frequency in the 4 groups, but no serious IMP-related AEs were observed. In addition, in the placebo, 2,000 JAU, 5,000 JAU and 10,000 JAU groups, there were 2 (0.8%), 7 (2.7%), 1 (0.4%), and 7 (2.7%) cases, respectively, that required discontinuation during the dose-finding period because of IMP-related AEs. The incidence of IMP-related AEs was 49.6%, 46.6%, and 54.8% in the 2,000, 5,000 and 10,000 JAU groups, respectively, revealing no major differences. With

the exception of 1 event in 1 participant (tendon rupture) in the placebo group, no severe AEs developed in this trial. Most IMP-related AEs were mild. Most of the participants recovered without treatment. The most frequent AEs were local reactions associated with the administration site, such as mouth edema, throat irritation, ear pruritus, oral pruritus, and oral discomfort. Details on common IMP-related AEs are available in the Results section and Table E8 in this article's Online Repository at www.jaci-inpractice.org. The cumulative incidence of IMP-related AEs from the start of treatment in the active groups was 57.4% within 2 weeks, 83.4% within 4 weeks, and 93.0% within 8 weeks.

The grading systems for systemic and local AEs in AIT advocated by the World Allergy Organization^{17,18} were used as references to calculate systemic and local AEs. Notably, there was no difference in terms of the incidence of systemic AEs among all groups, including the placebo group. Furthermore, there were no reports of grade 4 and 5 AEs, which correspond to anaphylaxis. Although the incidence rate of local AEs was higher in the active groups, there were no significant differences among them. Most local AEs required no treatment. During the dose-finding period in the placebo, 2,000 JAU, 5,000 JAU, and 10,000 JAU groups, the patients of 1 (0.4%), 0 (0%), 1 (0.4%), and 3 (1.2%) cases, respectively, had to discontinue the study because of the occurrence of grade 3 AEs. The incidence rate of IMP-related AEs among children aged 5 to 17 years in the placebo, 2,000 JAU, 5,000 JAU, and 10,000 JAU groups was 30.6%, 55.4%, 67.3%, and 63.0%, respectively, and that among elderly patients 50 years or older with prolonged histories of JC pollinosis in the placebo, 2,000 JAU, 5,000 JAU, and 10,000 JAU groups was 17.1%, 44.1%, 35.3%, and 52.5%, respectively.

The evaluation of efficacy during the dose-finding period demonstrated the superiority of the 2,000, 5,000 and 10,000 JAU groups over the placebo, revealing that the 5,000 and 10,000 JAU groups were equally effective and both were superior to the 2,000 JAU group. There was no difference in the safety profiles of all active groups. Therefore, 5,000 JAU was selected as the optimal dose.

Efficacy and safety during the long-term treatment period (second and third seasons)

Evaluations during the long-term treatment period were performed during the 2016 and 2017 JC pollen dispersion seasons. Daily averaged TNSMS during those periods are presented in Figure 3, B and C. The mean TNSMS of all groups fluctuated in conjunction with the JC pollen situation. Mean scores of the AP, PA, and AA groups were all lower than that of the PP group. TNSMS during the peak symptom periods in 2016 and 2017 are presented in Figure 5, A and B. The relative ratio to that of the PP group for the adjusted mean of TNSMS in the 2016 peak symptom period was 36.9% in the AP group, 32.8% in the PA group, and 45.1% in the AA group (all $P < .001$). For the 2017 peak symptom period, these ratios were 35.3%, 41.0%, and 45.9% in the AP, PA, and AA groups, respectively (all $P < .001$).

Results of the analysis of well-days,¹⁹ severe-symptom days,²⁰ and cumulative number of rescue medications used during 2017, which indicate clinical relevance, are presented in Table IV and Table E9 (available in this article's Online Repository at www.jaci-inpractice.org). These results are similar to those of TNSMS and showed a significant difference from the PP group (all $P < .05$).

TABLE IV. Symptom relief evaluation during the peak symptom period in the third season (FAS)

Generalized linear									
Evaluation	Treatment group	N	Probability (%)*	Against PP		Against AP		Against PA	
				Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Well-days†									
Peak symptom period	PP	145	30.0	—	—	—	—	—	—
	AP	73	43.4	1.79 (1.13-2.83)	.013	—	—	—	—
	PA	75	55.0	2.85 (1.79-4.52)	<.001	1.59 (0.95-2.67)	.077	—	—
	AA	146	57.4	3.14 (2.16-4.56)	<.001	1.76 (1.13-2.72)	.012	1.10 (0.71-1.71)	.664
JC pollen dispersion season	PP	145	41.5	—	—	—	—	—	—
	AP	73	53.1	1.60 (1.09-2.35)	.017	—	—	—	—
	PA	75	62.9	2.39 (1.59-3.61)	<.001	1.50 (0.95-2.37)	.085	—	—
	AA	146	66.0	2.74 (2.00-3.75)	<.001	1.72 (1.18-2.50)	.005	1.15 (0.77-1.71)	.508
Severe-symptom days‡									
Peak symptom period	PP	145	31.0	—	—	—	—	—	—
	AP	73	14.8	0.39 (0.22-0.68)	.001	—	—	—	—
	PA	75	10.4	0.26 (0.14-0.49)	<.001	0.67 (0.32-1.41)	.295	—	—
	AA	146	7.7	0.19 (0.10-0.33)	<.001	0.48 (0.24-0.96)	.039	0.71 (0.34-1.50)	.375
JC pollen dispersion season	PP	145	21.1	—	—	—	—	—	—
	AP	73	9.5	0.39 (0.23-0.69)	.001	—	—	—	—
	PA	75	7.2	0.29 (0.16-0.54)	<.001	0.74 (0.35-1.54)	.419	—	—
	AA	146	5.9	0.24 (0.14-0.41)	<.001	0.60 (0.31-1.18)	.137	0.81 (0.39-1.68)	.577

FAS, Full analysis set.

^{*}Calculated as total number of well-days or severe-symptom days/(number of participants multiplied by number of days during the peak symptom period).

[†]All symptoms (runny nose, blocked nose, sneezing, itchy eyes, and watery eyes) required to be – or 1+ without rescue medications.

[‡]Days with at least 1 symptom evaluated as 4+ for nasal symptoms or 3+ for ocular symptoms.

Details for results of general state evaluation using the JRQLQ are presented in the Results section and Figure E1, B and C, in the Online Repository. Statistically significant differences from the PP group in the second and third seasons were revealed in all groups that received active treatment. Similar to the results of TNSMS, the PA group improved more than the AP group in the third season, although the opposite result was seen in the second season.

AEs during the long-term treatment period were evaluated for the entire treatment population, to maintain blinding. Overall, discontinuation due to IMP-related AEs occurred in 2 (0.4%) cases. The total incidence of AEs in the treatment groups was 76.9%; the incidence of IMP-related AEs was 6.9%. As in the first season, no deaths or epinephrine administration occurred. Serious AEs were observed in 9 participants (1.9%); in all cases, a causal relationship with IMP was ruled out by the principal investigators. Two severe AEs (0.4%) were reported; the events (injury and malignant neoplasm of the lung) were assessed as not related to IMP. Of the AEs that developed during the long-term treatment period, 97.4% were mild. All IMP-related AEs that occurred during the long-term treatment period were also mild. The main IMP-related AEs, such as oral pruritus, throat irritation, and mouth edema, were characteristic of SLIT and were similar to those occurring during the dose-finding period. The cumulative incidence of IMP-related AEs after re-randomization was 57.7% within 2 weeks, 75.0% within 4 weeks, and 80.8% within 8 weeks.

DISCUSSION

This trial is the first large-scale field study to determine the optimal dose of SLIT for JC pollinosis using 3 active groups and a placebo group. To verify the reproducibility of the efficacy and disease-modifying effect of the JC pollen SLIT tablet, before the start of the second JC pollen dispersion season, participants in the placebo and 5000 JAU groups were reassigned.

In the first season, the absolute difference from the placebo group in the adjusted mean of TNSMS significantly improved in all active groups. The relative differences in TNSMS between the 3 active groups and the placebo group met the criterion of the World Allergy Organization, which requires at least 20% difference from placebo as the minimum clinically relevant effect.²¹ In addition, the upper limit of the 95% CI in all active groups met the criteria of the US Food and Drug Administration,²²⁻²⁴ with the exception of the greater than or equal to 10% upper limit of the 95% CI for the 2000 JAU group during the JC pollen season. All criteria for the total nasal and ocular symptom and medication score were also met during the same period.

To date, clinical field trials of SLIT using multiple doses of drugs (Grazax, Oralair, Acarizax, and Miticure)²⁵⁻²⁹ have reported significant improvement in the primary end point for all active drugs against placebo, but none of these trials has confirmed a dose-response with statistically significant differences between active groups. In this trial, patients aged 5 to 64 years with JC pollinosis were included. A comparison of the primary outcome measures of TNSMS and the incidence rate of IMP-

related AEs among all subjects, children (5-17 years) and adults (18-64 years), showed similar outcomes. Accordingly, we could set an optimal dose with a favorable safety profile across a wide age range; long-term treatment with this dose promises a clear disease-modifying effect.

From the second JC pollen season onward, a significant improvement in TNSMS was observed in the AA group compared with that in the PP group, and this improvement lasted into the third season. The relative ratio of the PP group to the AA group decreased from the first to the second seasons, and this decrease continued into the third season. The results of our efficacy evaluation are consistent with those previously reported.³⁰⁻³² This confirms the efficacy of the SLIT tablet as an AIT drug. Participants in the PA group, who took IMP for 3 months before the start of the second JC pollen dispersion season, showed significant improvement from 2016 (the first season of active treatment for the PA group) onward, compared with those in the PP group. This finding demonstrated reproducibility of the results obtained in the first season for the AA group. The second season for the AP group and the third season for the PA group both began in the JC pollen season following 15 months of taking IMP; therefore, the rates of improvement in TNSMS (AP 36.9% and PA 41.0%) showed good concordance. Reproducibility was also achieved during the long-term treatment period. The AP group took the drug for 15 months, followed by 3 months of taking placebo until the start of the JC pollen dispersion season, which indicates the validity of our results, with slightly lower values than in the PA group.

The AP group also showed significant improvement compared with the placebo group in the third season, 15 months after switching to placebo. This, therefore, demonstrated that the effect of taking the optimal dose for JC pollinosis for 15 months persists even 15 months later. Scadding et al³³ observed no lasting effect in their examination of efficacy during the season following completion of 2 years of SLIT for seasonal hay fever. The contradictory results in our trial are likely caused by different evaluation methods. Scadding et al evaluated effects using the nasal allergen challenge, whereas we evaluated effects by natural exposure in the field, using an electronic diary to gather information on symptom scores and medication use in a timely manner during the JC pollen season. Despite the effect of 5000 JAU lasting a further 15 months after 15 months of taking placebo in the AP group, the effect was lower than that in the AA group. This result indicates that SLIT offers continuing efficacy even after the completion of treatment; however, continuous long-term treatment has an even stronger effect.

Evaluations of well-days, severe-symptom days, and general state according to the JRQLQ in the third season were all significantly improved in the AP, PA, and AA groups compared with the PP group, both in the peak symptom period and in the JC dispersion pollen season. This improvement was greatest in the AA group, followed by the PA and AP groups. This result was consistent with those of TNSMS evaluation in the third season. Benefits to the patient, therefore, increased with increasing length of the treatment period.

IMP-related AEs that developed the entire treatment period were the same as those for previously reported SLIT formulations; therefore, no new safety information that should be reported was obtained during the 3 years of treatment. In addition, in the present trial, there was a lower number of discontinuation cases because of IMP-related AEs compared with that observed

in other studies.³⁴⁻³⁷ This might be attributable to the differences between the antigenicity of JC and other allergens.

In conclusion, the optimal dose for the JC pollen SLIT tablet in Japanese patients aged 5 to 64 years with JC pollinosis was determined, with a favorable safety profile. The optimal dose revealed clinically relevant effects without additional safety information over a 3-year treatment period. Results of the 2-year observational period are still expected, which will indicate the disease-modifying effect.

Acknowledgments

We present this publication on behalf of all the involved investigators. The trial was funded by Torii. We thank the clinical trial team at Torii for clinical project management, operational oversight, quality control, safety monitoring, data management, and statistical analyses. We thank Hendrik Nolte and Simon Andrew Lawton from ALK for reviewing the manuscript. We thank Edanz Group (www.edanzediting.com/ac) for the English language review. This assistance was funded by Torii, Tokyo, Japan.

REFERENCES

1. Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis: the national affliction. *J Allergy Clin Immunol* 2014;133:632-639.e635.
2. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003;91:288-96.
3. Kaneko Y, Motohashi Y, Nakamura H, Endo T, Eboshida A. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. *Int Arch Allergy Immunol* 2005;136:365-71.
4. Okamoto Y, Horiguchi S, Yamamoto H, Yonekura S, Hanazawa T. Present situation of cedar pollinosis in Japan and its immune responses. *Allergol Int* 2009;58:155-62.
5. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: January 27-29 1997. *Allergy* 1998;53:1-42.
6. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;62:943-8.
7. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008;101:206-11.
8. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010;126:969-75.
9. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63:8-160.
10. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018;141:529-538.e513.
11. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy* 2015;5:12.
12. Okubo K, Kuroki Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int* 2017;66:205-19.
13. Ohashi-Doi K, Kito H, Du W, Nakazawa H, Ipsen H, Gudmann P, et al. Bioavailability of house dust mite allergens in sublingual allergy tablets is highly dependent on the formulation. *Int Arch Allergy Immunol* 2017;174:26-34.
14. Yasueda H, Okuda M, Yoshida H, Ito K, Baba M, Iikura Y, et al. A basic policy for allergen standardization in our country and standardization of Japanese cedar (*Cryptomeria japonica*) pollen extracts. *Allergol Int* 1997;46:135-40.
15. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2015;166:177-88.
16. Okuda M, Ohkubo K, Goto M, Okamoto H, Konno A, Baba K, et al. Comparative study of two Japanese rhinoconjunctivitis quality-of-life questionnaires. *Acta Otolaryngol* 2005;125:736-44.
17. Cox LS, Sanchez-Borges M, Lockett RF. World Allergy Organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract* 2017;5:58-62.

18. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox LS, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy. *J Allergy Clin Immunol* 2013;132:93-8.
19. Worm M. 'Well days' after sublingual immunotherapy with a high-dose 6-grass pollen preparation. *Allergy* 2009;64:1104-5.
20. Durham SR, Birk AO, Andersen JS. Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy* 2011;66:120-3.
21. 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.
22. US Food and Drug Administration. Briefing document: Oralair. 26th Meeting of the Allergenic Products Advisory Committee; 2013. Available from: <https://wayback.archive-it.org/7993/20170114031525/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM381419.pdf>. Accessed April 26, 2018.
23. US Food and Drug Administration. Briefing document: Grastek. 26th Meeting of the Allergenic Products Advisory Committee; 2013. Available from: <https://wayback.archive-it.org/7993/20170114031528/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM381421.pdf>. Accessed April 26, 2018.
24. US Food and Drug Administration. Briefing document: Ragwitek. 27th Meeting of the Allergenic Products Advisory Committee; 2014. Available from: <https://wayback.archive-it.org/7993/20170113073043/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM385312.pdf>. Accessed April 26, 2018.
25. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
26. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80. 80.e71-2.
27. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambrosio L, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol* 2012;130:1327-1334.e1.
28. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016;137:444-451.e8.
29. 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;139:1840-1848.e10.
30. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125:131-138.e1-7.
31. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-725.e5.
32. Didier A, Mallin HJ, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy* 2013;43:568-77.
33. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial. *JAMA* 2017;317:615-25.
34. Didier A, Mallin HJ, Worm M, Horak F, Jäger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
35. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90.
36. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
37. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.

ONLINE REPOSITORY

METHODS

Outcomes measures

Construction of the scores used in the trial is presented in [Table E1](#), and each symptom was evaluated in compliance with Japanese guidelines for allergic rhinitis, 2017 ([Tables E2](#) and [E3](#)).

Sample size

The sample size for the dose-finding period was calculated on the basis of results of a previously reported study on JC pollen SLIT extracts.^{E1}

The severity of symptoms of JC pollinosis is known to be influenced by the volume of dispersed pollen. In the clinical trial for JC pollen SLIT extracts, the mean TNSMS of the placebo group during the peak symptom period was 8.61 in a year with a high JC pollen volume and 5.71 in a year with a low JC pollen volume. The combined SD of TNSMS for the JC pollen SLIT extracts and placebo groups in each year was 3.82 and 3.37, respectively. The mean TNSMS during the peak symptom period in the first season for the JC pollen SLIT extracts group was 18% lower than that for the placebo group.

Based on these results, estimates were calculated ([Table E4](#)) for the mean and SD of TNSMS for both the JC pollen SLIT tablet group and the placebo group, based on the JC pollen volume during the peak symptom period, assuming a mean TNSMS for the JC pollen SLIT tablet at 2,000, 5,000, and 10,000 JAU during the peak symptom period of −18%, −20%, and −22%, respectively, lower than that of the placebo group.

The calculated detection powers in each hypothetical scenario are presented in [Table E5](#) and are based on a simulation experiment using SAS software (SAS Institute, Cary, NC) and the 4 above-mentioned hypothetical means.

Given an analysis set of 200 patients, the detection power is greater or equal to 80% under any scenario. The target sample size was, therefore, set at 230 per group, with consideration of dropouts.

Statistical methodology

All statistical tests were performed using SAS Version 9.3, with the level of significance on both sides set to 5%.

The primary end point during the dose-finding period was TNSMS during the peak symptom period. Primary analysis was performed in the full analysis set and involved the use of a linear model with the treatment groups as explanatory variables. Restricted maximum likelihood was used for estimating the linear model. Paired comparisons were performed with the placebo group based on the least squares mean; a closed testing procedure, in which tests were performed sequentially from a high dose, was used to adjust for multiplicity in tests for these comparisons. Fieller theorem^{E2} was used for calculating the CI for the rate of decrease in the least squares mean. The total nasal and ocular symptom and medication score during the peak symptom period, which was a key secondary end point, was also subjected to the same analyses as the primary end point.

The following 3 analyses were conducted for primary and key secondary end points in the sensitivity analyses:

- A linear model analysis in the per-protocol set using treatment groups as explanatory variables.

- A linear mixed-effects model analysis in the full analysis set using treatment groups and age (<18 years or ≥18 years) as explanatory variables, and the medical institution implementing the trial as the random effect.
- Intergroup paired comparisons using the Wilcoxon rank-sum test (full analysis set).

JRQLQ scores were analyzed using the Wilcoxon rank-sum test.

The analysis during the long-term treatment period involved the same analyses as those during the dose-finding period, with each dose group from the dose-finding period reassigned into 4 new groups (PP, PA, AP, and AA groups).

RESULTS

JC pollen counts and evaluation period

Peak symptom periods were determined on the basis of pre-defined criteria, from March 15 to 31 in the dose-finding period, which was the first season, from March 9 to 29 in the second season, and from March 11 to 31 in the third season ([Table E6](#)).

Sensitivity analyses on the primary and key secondary end points in the primary evaluation period during the dose-finding period

The results of sensitivity analyses of TNSMS and total nasal and ocular symptom and medication score are presented in [Table E7](#). These results support the results of primary analysis that the 5,000 JAU and 10,000 JAU groups were superior to the 2,000 JAU group, in addition to the superiority of all active groups against the placebo group, though there was no difference between the 5,000 JAU and 10,000 JAU groups.

General state evaluation according to the JRQLQ

All active groups improved against the placebo group in the dose-finding period. When the proportions of “0” and “1” were observed during the general status evaluation, the percentages for the placebo, 2,000 JAU, 5,000 JAU, and 10,000 JAU groups were found to be 18.1%, 30.7%, 30.9%, and 37.0%, respectively. After re-randomization, participants in all groups that received active treatment showed clear benefit against the placebo group throughout the trial up to that point. Furthermore, when the proportions of “0” and “1” were observed during the general status evaluation, the percentages for the PP, PA, AP, and AA groups were found to be 24.8%, 43.7%, 37.9%, and 41.2%, respectively, in the second year and 29.5%, 50.0%, 42.6%, and 56.4%, respectively, in the third year ([Figure E1](#)).

Common IMP-related AEs

Most IMP-related AEs were local events at the application site such as mouth edema, throat irritation, ear pruritus, oral pruritus, and oral discomfort. There were no large differences in observed events and incidences among the active groups ([Table E8](#)).

Cumulative frequency of rescue medication use

[Table E9](#) presents the cumulative frequency of rescue medication use during each observed season. For all seasons, the frequency of rescue medication use decreased significantly in the active treatment groups than in the placebo group.

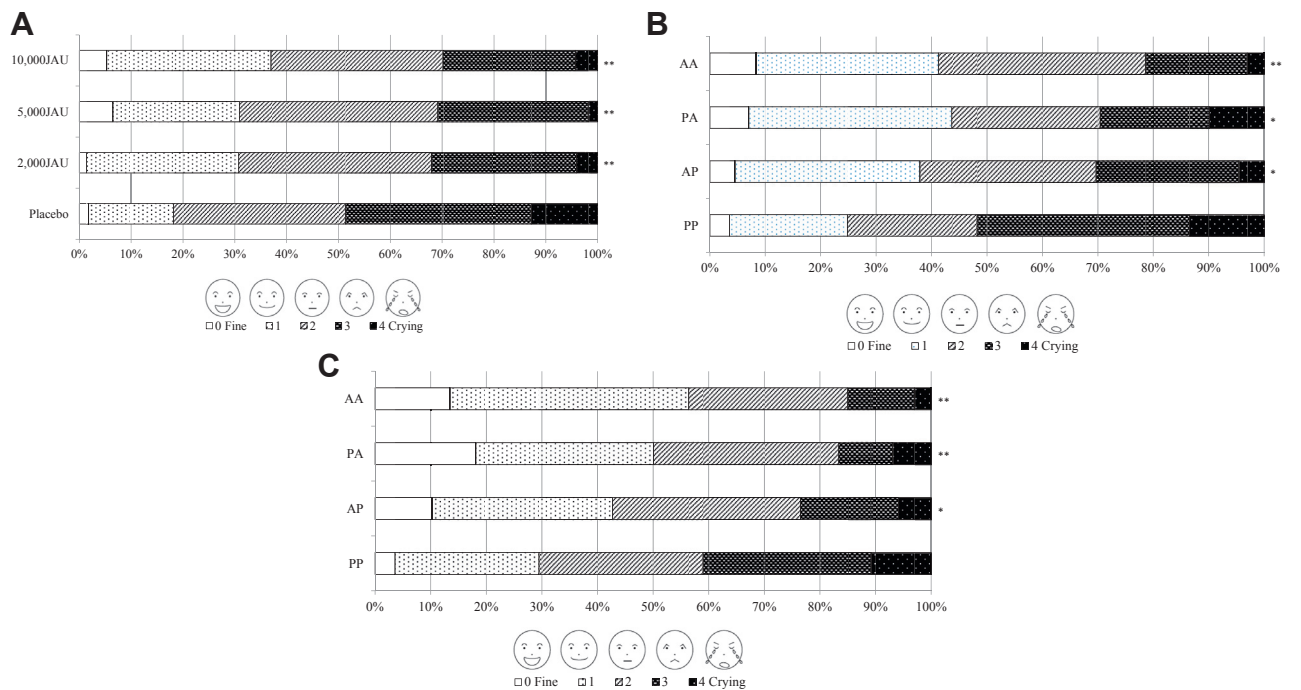


FIGURE E1. General state evaluation using the JRQLQ in the dose-finding period (A), the second season (B), and the third season (C) (FAS). After determining the optimal dose before the second season, participants in the 2,000 JAU and 10,000 JAU groups discontinued the trial; participants in the 5,000 JAU and placebo groups were re-randomized at a ratio of 2:1 to a group that continued to receive the same doses (AA, active → active; PP, placebo → placebo) or a group switched to different doses (AP, active → placebo; PA, placebo → active). FAS, Full analysis set. * $P < .01$, ** $P < .001$.

TABLE E1. Construction of scores used in the trial

Symptom	TNSMS	TNOSMS
Runny nose	0-4	0-4
Sneezing	0-4	0-4
Blocked nose	0-4	0-4
Itchy eyes	—	0-3
Watery eyes	—	0-3
Oral antihistamine	0 = not used or 3 = used	0 = not used or 3 = used
Nasal spray	0 = not used or 3 = used	0 = not used or 3 = used
Ocular antihistamine	—	0 = not used or 3 = used
Total	0-18	0-27

TNOSMS, Total nasal and ocular symptom and medication score.

TABLE E2. Rhinitis symptom evaluation and score

Symptom	Score				
	4	3	2	1	0
Runny nose	≥21 times	11-20 times	6-10 times	1-5 times	0
Sneezing	≥21 times	11-20 times	6-10 times	1-5 times	0
Blocked nose	Completely obstructed all day	Very severe nasal blockage causing prolonged oral breathing in a day	Severe nasal blockage causing occasional oral breathing in a day	Nasal blockage without oral breathing	No trouble

TABLE E3. Conjunctivitis symptom evaluation and score

Symptom	Score			
	3	2	1	0
Itchy eyes	Intolerably itchy	Very itchy	Slightly itchy	No trouble
Watery eyes	Cannot do regular tasks	Very watery	Not very watery	No trouble

TABLE E4. Simulation pattern of TNSMS based on the results of JC pollen SLIT extracts trial

Amount of JC pollen dispersed	Statistic	JC pollen SLIT tablet			Placebo
		2,000 JAU	5,000 JAU	10,000 JAU	
High	Mean	7.06	6.89	6.71	8.61
	SD			3.82	
Low	Mean	4.67	4.56	4.45	5.71
	SD			3.37	

TABLE E5. Power for statistical analysis

Amount of JC pollen dispersed	No. of participants	Power (%)		
		vs 2,000 JAU	vs 5,000 JAU	vs 10,000 JAU
High	200	97.9	99.4	99.9
Low	200	80.7	89.5	96.0

TABLE E6. JC pollen counts and evaluation period

<u>JC pollen dispersion season</u>		<u>Peak symptom period</u>
<u>Year</u>	<u>(JC pollen counts)</u>	<u>(JC pollen counts)</u>
2015	February 11 to April 25 (3893 grains/cm ²)	March 15 to March 31 (1537 grains/cm ²)
2016	February 13 to April 23 (2995 grains/cm ²)	March 9 to March 29 (1569 grains/cm ²)
2017	February 16 to April 26 (2895 grains/cm ²)	March 11 to March 31 (1359 grains/cm ²)

TABLE E7. Sensitivity analyses of the primary end point (TNSMS) and key secondary end point (TNOSMS) in the primary evaluation period

Analysis set	Treatment group	N	LS mean	Absolute difference from placebo (95% CI) Relative difference to placebo (95% CI)	P value	Absolute difference from 2,000 JAU (95% CI) Relative difference to 2,000 JAU (95% CI)	P value	Absolute difference from 5,000 JAU (95% CI) Relative difference to 5,000 JAU (95% CI)	P value
TNSMS									
FAS	Linear mixed effects								
	Placebo	257	7.08	—	—	—	—	—	—
	2,000 JAU	248	5.60	1.48 (0.89 to 2.06) 20.9% (13.1% to 28.2%)	<.001	—	—	—	—
	5,000 JAU	255	4.85	2.23 (1.65 to 2.81) 31.5% (24.1% to 38.4%)	<.001	0.75 (0.17 to 1.33) 13.4% (3.1% to 22.7%)	.012	—	—
	10,000 JAU	245	4.89	2.19 (1.60 to 2.77) 30.9% (23.4% to 38.0%)	<.001	0.71 (0.12 to 1.30) 12.7% (2.3% to 22.2%)	.019	−0.04 (−0.63 to 0.54) −0.8% (−13.8% to 10.6%)	.891
PPS	Linear								
	Placebo	257	7.01	—	—	—	—	—	—
	2,000 JAU	248	5.50	1.51 (0.91 to 2.10) 21.5% (13.6% to 28.9%)	<.001	—	—	—	—
	5,000 JAU	255	4.74	2.27 (1.68 to 2.86) 32.3% (24.9% to 39.3%)	<.001	0.76 (0.16 to 1.36) 13.8% (3.1% to 23.4%)	.013	—	—
	10,000 JAU	245	4.81	2.20 (1.60 to 2.79) 31.4% (23.8% to 38.5%)	<.001	0.69 (0.09 to 1.29) 12.6% (1.7% to 22.4%)	.025	−0.07 (−0.66 to 0.53) −1.4% (−15.0% to 10.5%)	.824
TNOSMS									
FAS	Linear mixed effects								
	Placebo	257	9.77	—	—	—	—	—	—
	2,000 JAU	248	7.38	2.39 (1.57 to 3.20) 24.4% (16.7% to 31.7%)	<.001	—	—	—	—
	5,000 JAU	255	6.43	3.34 (2.53 to 4.14) 34.1% (26.8% to 41.1%)	<.001	0.95 (0.13 to 1.76) 12.9% (1.9% to 22.8%)	.023	—	—
	10,000 JAU	245	6.42	3.35 (2.53 to 4.16) 34.3% (26.8% to 41.3%)	<.001	0.96 (0.13 to 1.78) 13.0% (1.9% to 23.0%)	.023	0.01 (−0.81 to 0.83) 0.2% (−13.4% to 12.1%)	.981
PPS	Linear								
	Placebo	257	9.69	—	—	—	—	—	—
	2,000 JAU	248	7.27	2.42 (1.59 to 3.24) 24.9% (17.1% to 32.2%)	<.001	—	—	—	—
	5,000 JAU	255	6.31	3.38 (2.56 to 4.20) 34.9% (27.5% to 41.8%)	<.001	0.96 (0.13 to 1.79) 13.2% (2.0% to 23.3%)	.023	—	—
	10,000 JAU	245	6.33	3.36 (2.53 to 4.19) 34.6% (27.2% to 41.7%)	<.001	0.94 (0.10 to 1.78) 12.9% (1.5% to 23.2%)	.028	−0.02 (−0.85 to 0.81) −0.3% (−14.4% to 12.1%)	.961

End point	Treatment group	N	Median	Nonparametric analysis					
				Hodges-Lehmann estimator (95% CI)	P value*	Hodges-Lehmann estimator (95% CI)	P value*	Hodges-Lehmann estimator (95% CI)	P value*
TNSMS (FAS)	Placebo	257	6.53	—	—	—	—	—	—
	2,000 JAU	248	4.56	1.28 (0.65 to 1.88)	<.001	—	—	—	—
	5,000 JAU	255	4.29	1.74 (1.18 to 2.35)	<.001	0.44 (0.00 to 0.88)	.053	—	—
	10,000 JAU	245	3.88	1.88 (1.29 to 2.53)	<.001	0.65 (0.18 to 1.06)	.006	0.24 (−0.18 to 0.59)	.289
TNOSMS (FAS)	Placebo	257	8.76	—	—	—	—	—	—
	2,000 JAU	248	6.12	2.06 (1.23 to 2.92)	<.001	—	—	—	—
	5,000 JAU	255	5.65	2.65 (1.88 to 3.47)	<.001	0.53 (−0.10 to 1.13)	.090	—	—
	10,000 JAU	245	5.00	2.88 (2.12 to 3.76)	<.001	0.88 (0.24 to 1.47)	.006	0.35 (−0.18 to 0.92)	.189

FAS, Full analysis set; TNOSMS, Total nasal and ocular symptom and medication score; LS, least squares; PPS, per-protocol analysis set.

*Wilcoxon rank-sum test.

TABLE E8. IMP-related AEs with an incidence of >2% in active groups (dose-finding period)

IMP-related AEs	Placebo (N = 259)			2,000 JAU (N = 260)			5,000 JAU (N = 264)			10,000 JAU (N = 259)			Active all (N = 783)		
	E	N	%	E	N	%	E	N	%	E	N	%	E	N	%
Mouth edema	—	—	—	31	27	10.4	41	39	14.8	49	47	18.1	121	113	14.4
Throat irritation	8	6	2.3	44	40	15.4	37	31	11.7	48	41	15.8	129	112	14.3
Ear pruritus	5	5	1.9	32	30	11.5	36	32	12.1	41	36	13.9	109	98	12.5
Oral pruritus	—	—	—	17	16	6.2	30	28	10.6	24	23	8.9	71	67	8.6
Oral discomfort	—	—	—	11	11	4.2	20	18	6.8	18	18	6.9	49	47	6.0
Oropharyngeal discomfort	3	3	1.2	12	12	4.6	15	12	4.5	20	16	6.2	47	40	5.1
Rhinorrhea	17	16	6.2	12	11	4.2	9	9	3.4	18	16	6.2	39	36	4.6
Stomatitis	11	6	2.3	11	10	3.8	11	9	3.4	9	9	3.5	31	28	3.6
Eye pruritus	8	8	3.1	12	11	4.2	7	7	2.7	12	10	3.9	31	28	3.6
Sneezing	5	5	1.9	6	5	1.9	7	7	2.7	13	12	4.6	26	24	3.1
Laryngeal discomfort	4	3	1.2	6	6	2.3	7	7	2.7	9	6	2.3	22	19	2.4
Nasal congestion	13	11	4.2	5	5	1.9	4	4	1.5	10	10	3.9	19	19	2.4
Pruritus	4	2	0.8	12	10	3.8	6	5	1.9	3	3	1.2	21	18	2.3
Oral mucosal erythema	—	—	—	4	4	1.5	6	6	2.3	8	8	3.1	18	18	2.3

E, Number of events; N, number of participants; %, percentage of participants with adverse events.

TABLE E9. Cumulative number of rescue medication use during JC pollen dispersion season in the first, second, and third seasons (FAS)

				Nonparametric analysis
End point	Treatment group	N	Mean ± SD	P value (Wilcoxon rank-sum test against the placebo group or the PP group)
First season				
Oral antihistamine use	Placebo	257	10.2 ± 19.1	—
	2,000 JAU	248	6.6 ± 17.5	<.001
	5,000 JAU	255	2.4 ± 9.8	<.001
	10,000 JAU	245	4.7 ± 14.5	<.001
Nasal spray use	Placebo	257	10.2 ± 27.3	—
	2,000 JAU	248	4.8 ± 17.6	.002
	5,000 JAU	255	3.0 ± 15.4	<.001
	10,000 JAU	245	3.8 ± 18.0	<.001
Ocular antihistamine use	Placebo	257	13.0 ± 26.2	—
	2,000 JAU	248	6.4 ± 17.4	<.001
	5,000 JAU	255	4.0 ± 11.3	<.001
	10,000 JAU	245	4.4 ± 16.6	<.001
Second season				
Oral antihistamine use	PP	155	12.6 ± 23.8	—
	AP	76	2.9 ± 11.4	<.001
	PA	79	5.1 ± 12.6	.051
	AA	153	2.3 ± 8.6	<.001
Nasal spray use	PP	155	12.7 ± 35.6	—
	AP	76	2.3 ± 10.2	.014
	PA	79	2.9 ± 9.6	.080
	AA	153	2.0 ± 11.6	.006
Ocular antihistamine use	PP	155	17.1 ± 33.8	—
	AP	76	6.5 ± 23.6	<.001
	PA	79	4.6 ± 14.7	.001
	AA	153	3.4 ± 11.6	<.001
Third season				
Oral antihistamine use	PP	145	11.6 ± 23.6	—
	AP	73	2.2 ± 9.1	<.001
	PA	75	3.2 ± 11.2	<.001
	AA	146	3.2 ± 14.1	<.001
Nasal spray use	PP	145	13.7 ± 40.7	—
	AP	73	1.5 ± 7.6	.008
	PA	75	2.7 ± 13.6	.006
	AA	146	3.2 ± 19.5	<.001
Ocular antihistamine use	PP	145	12.4 ± 29.2	—
	AP	73	4.9 ± 17.3	.001
	PA	75	4.3 ± 16.3	.001
	AA	146	3.6 ± 18.8	<.001

FAS, Full analysis set.

REFERENCES

- E1. Okamoto Y, Okubo K, Yonekura S, Hashiguchi K, Goto M, Otsuka T, et al. Efficacy and safety of sublingual immunotherapy for two seasons in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2015; 166:177-88.
- E2. Fieller EC. Some problems in interval estimation. *J Roy Stat Soc B* 1954;16: 175-85.