



Contents lists available at ScienceDirect

Allergy International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Japanese cedar pollen sublingual immunotherapy is effective in treating seasonal allergic rhinitis during the pollen dispersal period for Japanese cedar and Japanese cypress

Dear Editor,

In Japan, allergic rhinitis is one of the most prevalent allergic diseases, and there has been an increase in seasonal allergic rhinitis in recent years.^{1,2} Matsubara *et al.* reported that the overall prevalence of allergic rhinitis was 49.2%, with a marked increase in Japanese cedar (JC) pollinosis among teenagers.² Over the past 20 years, the prevalence of JC pollinosis increased from 16.2% in 1998 to 26.5% in 2008 and 38.8% in 2019, and that of non-JC pollinosis also increased from 10.9% to 15.4% and 25.1%, respectively.² It is assumed that this may reflect an increase in Japanese cypress (JCY) pollinosis, in addition to increases in grass pollinosis and Asteraceae pollinosis.³

JC pollinosis is a typical type I allergic disease in which nasal, ocular, pharyngeal, and skin symptoms occur during the JC pollen dispersal season. JC pollinosis significantly affects daily activity, work productivity, learning, sleep, and quality of life. Furthermore, approximately 70% of patients with JC pollinosis are also allergic to JCY pollen.¹ It has been reported that almost all cases positive for specific immunoglobulin E (sIgE) antibody against JCY (JCY-sIgE) also have sIgE antibody against JC (JC-sIgE), and patients who are positive for only JCY-sIgE, i.e., negative for JC-sIgE, are rare.⁴ Recently, seasonal allergic rhinitis with JCY pollen dispersal has attracted attention, and its clinical relevance to JC pollinosis has been described. Because of the overlap of the dispersal period of JC pollen and that of JCY pollen, patients with combined JC and JCY pollinosis experience severe symptoms from February to April, when cedar pollen is dispersed, as well as from April to May, when cypress pollen is dispersed. Therefore, it is important to control their symptoms during this long period.

JC pollen sublingual immunotherapy (SLIT) tablets are available for use against JC pollinosis in Japan. These tablets are fast-dissolving, freeze-dried tablets containing JC pollen allergen extracts, including the major allergens, Cry j 1 and Cry j 2; these two allergens have strong amino acid sequence homology with the major allergens of JCY pollen, Cha o 1 and Cha o 2, respectively.⁵ In the field of marketing authorization for industrially manufactured allergen products in Europe, the concept of homologous groups has been introduced by the European Medical Agency.⁶ According to this concept, the data of one allergen extract demonstrating stability, efficacy, and safety can, to a limited extent, be

extrapolated to other allergen extracts belonging to the same homologous groups.^{6,7} Cedar and cypress are homologous groups of tree species within the family Cupressaceae.⁷ However, the clinical efficacy of JC pollen SLIT tablets for allergic symptoms with JCY pollen dispersal has been controversial in actual clinical settings. Here, we report the efficacy of JC pollen SLIT tablets against seasonal allergic rhinitis during the JC pollen and JCY pollen dispersal periods from a phase II/III study (JapicCTI no. 142579).

This randomized, double-blinded, placebo-controlled phase II/III trial was conducted to investigate the optimal dose of JC pollen SLIT tablets and examine the long-term efficacy and safety over 3 years with the selected dose and during a 2-year follow-up. We have already reported the beneficial sustained efficacy of JC pollen SLIT tablets in a treatment duration-dependent manner when using the total nasal symptom and medication score (TNSMS) during the peak symptom period for JC pollen as the primary endpoint.^{8,9} Here, we show the TNSMS of patients who consumed placebo SLIT tablets (Placebo group, $n = 159$) or SLIT tablets containing 5000 Japanese allergy units (JAU) of JC pollen (5000 JAU group, $n = 158$) for 3 years. The daily average TNSMS in the 5000 JAU group was consistently lower than that in the Placebo group during the JC pollen and JCY pollen dispersal period in all three seasons (Fig. 1A). Notably, the degree of increase in TNSMS in the 5000 JAU group was lower than that in the Placebo group in the third season, especially as the JCY pollen dispersed increasingly more (JCY pollen had a higher peak value compared with JC pollen) (Fig. 1A, third season). A relative reduction in TNSMS compared with the Placebo group was seen in the 5000 JAU group in a treatment duration-dependent manner (first, second, and third seasons: 28.6%, 40.2%, and 42.8% vs Placebo, respectively; $p < 0.001$, Fig. 1B). The total ocular symptom and medication score (TOSMS), examined as a secondary endpoint, also showed similar beneficial outcomes in the 5000 JAU group compared with the Placebo group (Fig. 2). These results suggest that JC pollen SLIT tablets sustained a clinically relevant effect against seasonal allergic rhinitis during not only the JC pollen dispersal period but also the JCY pollen dispersal period. Furthermore, the 5000 JAU group had significantly reduced TNSMS with clinically relevant effects compared with Placebo group even when evaluated separately for the JC pollen dispersal period and the JCY pollen dispersal period which was tentatively defined as after the day the JCY pollen count exceeded 30 grains/

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2021.08.012>1323–8930/Copyright © 2021, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article as: Yonekura S et al., Japanese cedar pollen sublingual immunotherapy is effective in treating seasonal allergic rhinitis during the pollen dispersal period for Japanese cedar and Japanese cypress, Allergy International, <https://doi.org/10.1016/j.alit.2021.08.012>

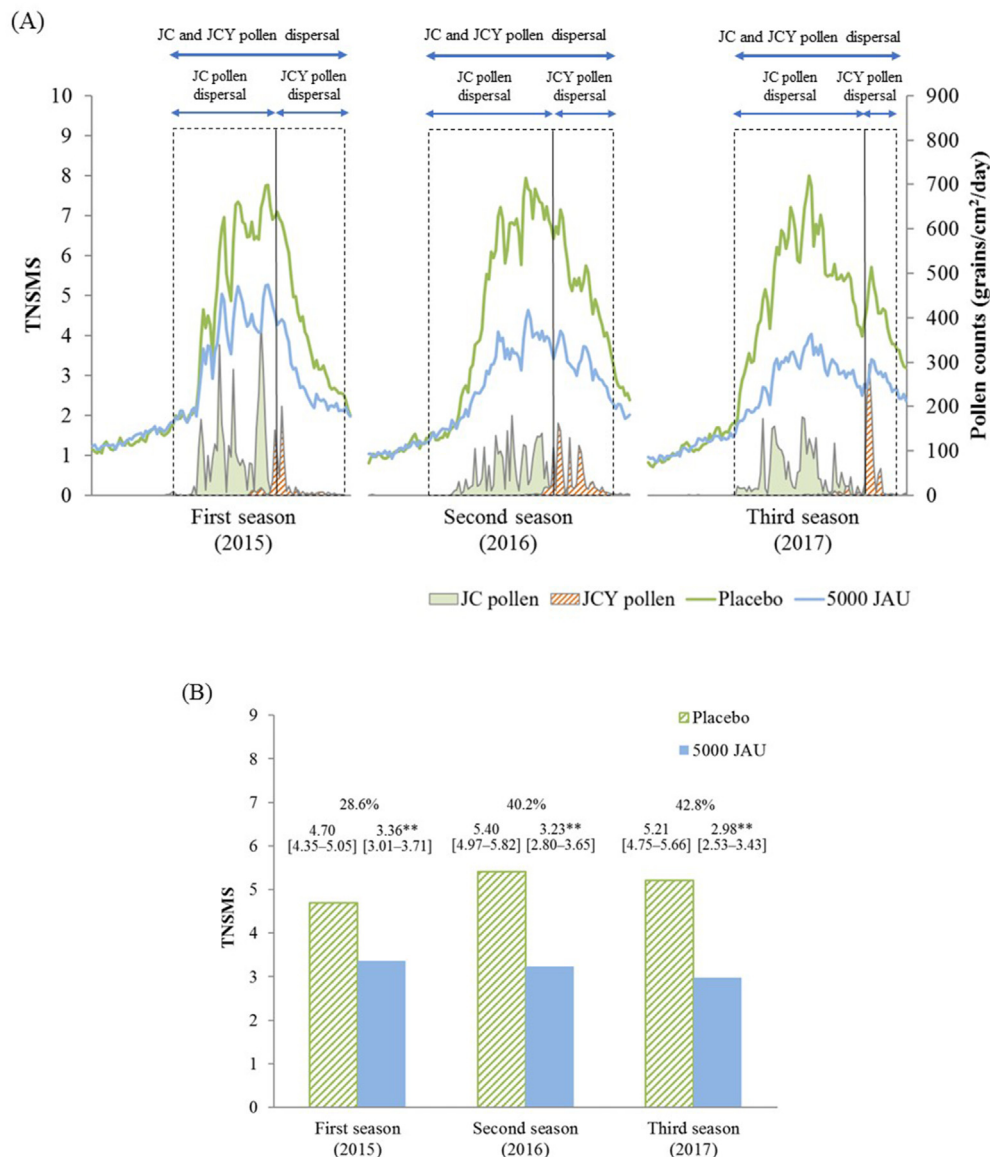


Fig. 1. (A) Daily average total nasal symptom and medication score (TNSMS) during the Japanese cedar (JC) pollen and Japanese cypress (JCY) pollen dispersal period in the first (2015), second (2016), and third (2017) study seasons. The JC and JCY pollen counts are indicated by green shading and orange striped shading, respectively. Placebo, subjects received placebo throughout the 3-year study; 5000 JAU, subjects received 5000 Japanese allergy units (JAU) throughout the 3-year study. The JC and JCY pollen counts in central Tokyo were measured using a Durham sampler. For JC pollen, the cumulative counts throughout the 3-year study (3892, 2994, and 2894 grains/cm², respectively) were in line with the count of the average year. JCY pollen counts throughout the 3-year study (815, 1221, and 1041 grains/cm², respectively) were also in line with the count of the average year. (B) Least squares means of TNSMS with 95% confidence intervals and relative differences (%) to Placebo during the JC and JCY pollen dispersal periods in the first (February 11 to April 25), second (February 13 to April 23), and third (February 16 to April 26) study seasons. **p < 0.001 vs Placebo. The JC and JCY pollen dispersal periods for the analysis were defined as starting on the first day of the first two consecutive days after January 1 on which there was a JC pollen count of over 1 grain/cm²/day, and ending on the day before the first of three consecutive days on which there was a JC pollen count of 0 grain/cm²/day, which included JCY pollen dispersal. The JCY pollen dispersal period was tentatively defined as after the day the JCY pollen count exceeded 30 grains/cm²/day, a greater impact on symptoms caused by JCY pollen than JC pollen, because of the overlap between the JC pollen dispersal periods and JCY pollen dispersal periods (2015; March 27, 2016; March 28, 2017; April 13).

cm²/day, a greater impact on symptoms caused by JCY pollen than JC pollen, because of the overlap between the JC pollen and JCY pollen dispersal periods (Supplementary Table 1).

Recently, a new major allergen of JCY pollen, Cha o 3, was discovered, and it has strong amino acid sequence homology with the major allergen of JC pollen, Cry j 4.^{10,11} Osada *et al.* reported that a low amount of Cry j 4 is included in JC pollen allergen extracts.¹¹ However, the extent to which Cha o 1, Cha o 2, and Cha o 3 each contribute to the clinical symptoms with JCY pollen dispersal are not fully understood. In the present study, approximately 80% of the patients

in both the Placebo and 5000 JAU groups were positive (≥ 0.7 kUA/L) for JCY-sIgE antibodies at baseline (Supplementary Table 2), but the presence or absence of historical clinical symptoms to JCY pollen in each subject was not confirmed. However, even when JCY-sIgE positive patients alone were analyzed, the relative reductions in TNSMS and TOSMS in the 5000 JAU group were significantly lower than for Placebo group during the JC pollen and JCY pollen dispersal periods over three seasons. In addition, similar results were observed when JCY-sIgE pseudo-positive (≥ 0.35 kUA/L) patients were included (Supplementary Fig. 1). The remaining approximately 20%

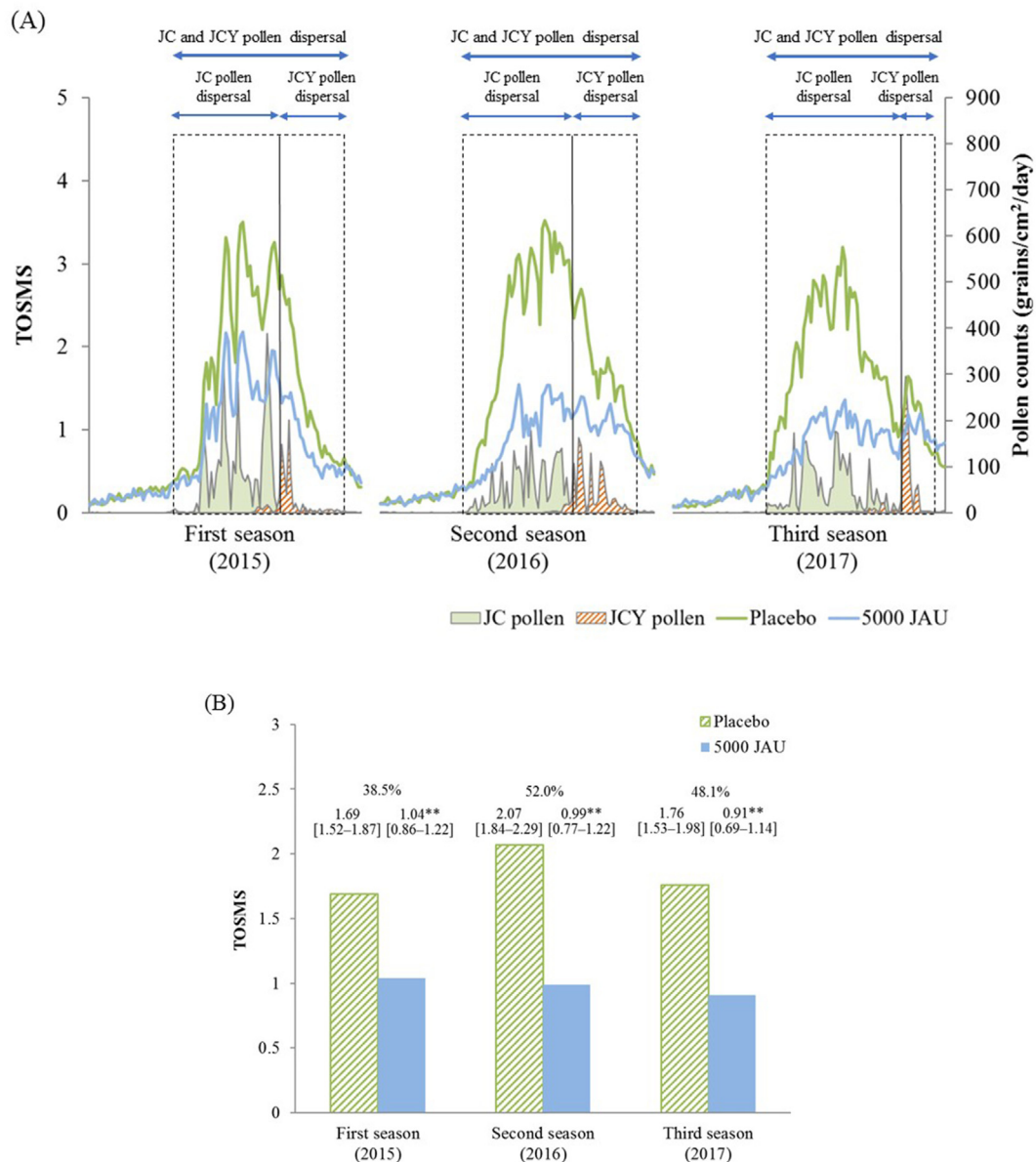


Fig. 2. (A) Daily average total ocular symptom and medication score (TOSMS) during the Japanese cedar (JC) pollen and Japanese cypress (JCY) pollen dispersal periods in the first (2015), second (2016), and third (2017) study seasons. JC pollen counts and JCY pollen counts are indicated by green shading and orange striped shading, respectively. Placebo, subjects received placebo throughout the 3-year study; 5000 JAU, subjects received 5000 Japanese allergy units (JAU) throughout the 3-year study. The JC and JCY pollen counts in central Tokyo were measured using a Durham sampler. For JC pollen, the cumulative counts throughout the 3-year study (3892, 2994, and 2894 grains/cm², respectively) were in line with the count of the average year. JCY pollen counts throughout the 3-year study (815, 1221, and 1041 grains/cm², respectively) were also in line with the count of the average year. (B) Least squares means of TOSMS with 95% confidence intervals and relative differences (%) to Placebo during the JC pollen and JCY pollen dispersal period in the first (February 11 to April 25), second (February 13 to April 23), and third (February 16 to April 26) study seasons. **p < 0.001 vs Placebo. The JC and JCY pollen dispersal periods for the analysis were defined as starting on the first day of the first two consecutive days after January 1 on which there was a JC pollen count of over 1 grain/cm²/day, and ending on the day before the first of three consecutive days on which there was a JC pollen count of 0 grain/cm²/day, which included JCY pollen dispersal. The JCY pollen dispersal period was tentatively defined as after the day the JCY pollen count exceeded 30 grains/cm²/day, a greater impact on symptoms caused by JCY pollen than JC pollen, because of the overlap between the JC pollen dispersal periods and JCY pollen dispersal periods (2015; March 27, 2016; March 28, 2017; April 13).

of patients who were negative (<0.7 kUA/L) for JCY-sIgE in the Placebo group also increased both their TNSMS and TOSMS in a manner similar to that of Placebo group subjects positive for JCY-sIgE, depending on the JCY pollen dispersal throughout the study, while the score of TOSMS were generally low in the subjects who were negative for JCY-sIgE. It is presumed that JC pollinosis patients who are negative for JCY-sIgE are immunologically affected by JCY pollen

because of the common allergen between JC pollen and JCY pollen. This suggests that it is important to handle allergic symptoms caused by JC pollen and JCY pollen not separately but comprehensively as cedar-cypress combined pollinosis.

This phase II/III study was conducted in the Tokyo metropolitan area. Because the area of cypress plantations is larger in western Japan, the amount of JCY pollen dispersed in western Japan was

estimated to be larger than that in eastern Japan, including Tokyo. However, over the past 10 years (2009–2018), including the present evaluation period, the amount of JCY pollen dispersed in the Tokyo metropolitan area was equal to or greater than that in western Japan.¹² The ratio of JCY pollen to the total dispersal amount of JC pollen and JCY pollen was higher in western Japan (approximately 50%) than that in the Tokyo metropolitan area (20%–30%); therefore, in addition to the clinical relevance of the ratio of JCY pollen, the impact of the JCY pollen dispersal pattern, large amounts over several days, will be anticipated in the future. Here, we found that JC pollen SLIT tablets were effective at treating seasonal allergic rhinitis during the pollen dispersal period for Japanese cedar and Japanese cypress, as well as in the individual JC pollen and JCY pollen dispersal periods. Thus, we will examine the efficacy of JC pollen SLIT tablets in patients with clinical symptoms triggered by JCY pollen to further determine the usefulness of JC pollen SLIT tablets for treating combined JC and JCY pollinosis, which is the same homologous group.

Acknowledgements

This trial was funded by Torii Pharmaceutical Co., Ltd., Tokyo, Japan.

We thank all involved investigators for their work done in relation to this trial. We also thank Katie Oakley, PhD, from Edanz Group (<https://en-author-services.edanz.com/ac>) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.08.012>.

Conflict of interest

MG has received honoraria from Taiho, Hisamitsu, Meiji Seika Pharma, and Novartis. KO has received a consultancy fee, honoraria, writing fee, and scholarship donation from Torii. YO has received a consultancy fee and honoraria from Torii. YM is an employee of Torii. SY, MO, and TK have no conflict of interest.

Syuiji Yonekura ^a, Minoru Gotoh ^b, Mitsuhiro Okano ^c, Tomoya Kurokawa ^{a,d}, Yuriko Maekawa ^{e,*}, Kimihiro Okubo ^b, Yoshitaka Okamoto ^{a,f}

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

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

^c Department of Otorhinolaryngology, International University of Health and Welfare, Chiba, Japan

^d Clinical Research Center, Chiba University Hospital, Chiba, Japan

^e Department of Medical Affairs, Torii Pharmaceutical Co., Ltd., Tokyo, Japan

^f Chiba Rousai Hospital, Chiba, Japan

* Corresponding author. Medical Affairs Department, Torii Pharmaceutical Co., Ltd., 3–4–1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan.
E-mail address: yuriko.maekawa@torii.co.jp (Y. Maekawa).

References

- Yamada T, Saito H, Fujieda S. Present state of Japanese cedar pollinosis: the national affliction. *J Allergy Clin Immunol* 2014;**133**:632–9. e5.
- Matsubara A, Sakashita M, Gotoh M, Kawashima K, Matsuoka T, Kondo S, et al. [Epidemiological survey of allergic rhinitis in Japan 2019]. *Nippon Jibiinkoka Gakkai Kaiho (Tokyo)* 2020;**123**:485–90 (in Japanese).
- Okubo K. [Practical Guideline for the Management of Allergic Rhinitis in Japan]. Revised 9th ed. Tokyo: Japan Society of Immunology and Allergology in Otolaryngology; 2020 (in Japanese).
- Ganbo T, Hisamatsu K, Inoue H, Kitta Y, Nakajima M, Goto R, et al. Detection of specific IgE antibodies to Japanese cypress pollen in patients with nasal allergy: a comparative study with Japanese cedar. *Auris Nasus Larynx* 1995;**22**:158–64.
- Suzuki M, Komiyama N, Itoh M, Sone T, Kino K, Takagi I, et al. Purification, characterization and molecular cloning of cha o 1, a major allergen of *Chamaecyparis obtusa* (Japanese cypress) pollen. *Mol Immunol* 1996;**33**:451–60.
- European Medicines Agency. Committee for Medicinal Products for Human Use Guideline on allergen products: production and quality issues EMEA/CHMP/BWP/304831/2007. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-allergen-products-production-quality-issues_en.pdf.
- Lorenz AR, Lüttkopf D, May S, Scheurer S, Vieths S. The principle of homologous groups in regulatory affairs of allergen products—a proposal. *Int Arch Allergy Immunol* 2009;**148**:1–17.
- Gotoh M, Yonekura S, Imai T, Kaneko S, Horikawa E, Konno A, et al. Long-term efficacy and dose-finding trial of Japanese cedar pollen sublingual immunotherapy tablet. *J Allergy Clin Immunol Pract* 2019;**7**:1287–97.
- Yonekura S, Gotoh M, Kaneko S, Kanazawa K, Takeuji Y, Okubo K, et al. Treatment duration-dependent efficacy of Japanese cedar pollen sublingual immunotherapy: evaluation of a phase II/III trial over three pollen dispersal seasons. *Allergol Int* 2019;**68**:494–505.
- Osada T, Harada T, Asaka N, Haruna T, Kino K, Sasaki E, et al. Identification and gene cloning of a new major allergen Cha o 3 from *Chamaecyparis obtusa* (Japanese cypress) pollen. *J Allergy Clin Immunol* 2016;**138**:911–3. e7.
- Osada T, Tanaka Y, Yamada A, Sasaki E, Utsugi T. Identification of cha o 3 homolog cry j 4 from *Cryptomeria japonica* (Japanese cedar) pollen: limitation of the present Japanese cedar-specific ASIT. *Allergol Int* 2018;**67**:467–74.
- Ministry of the Environment. [Pollinosis Environmental Health Manual 2019]. Available from: https://www.env.go.jp/chemi/anzen/kafun/manual/2019_full.pdf (in Japanese).

Received 30 March 2021

Received in revised form 21 July 2021

Accepted 30 July 2021

Available online xxx

Supplementary Table 1.

Analytical results of the total nasal symptom and medication score (TNSMS) in the Japanese cedar pollen dispersal period and Japanese cypress pollen dispersal period for the full analysis set

Treatment group	N	Japanese cedar pollen dispersal period			Japanese cypress pollen dispersal period		
		Least squares mean (95% CI)	Absolute difference vs Placebo (95% CI)	P-value	Least squares mean (95% CI)	Absolute difference vs Placebo (95% CI)	P-value
			Relative difference vs Placebo (95% CI)			Relative difference vs Placebo (95% CI)	
First season (2015) (Linear model analysis [†])							
Placebo	159	4.88 (4.53 to 5.23)	—	—	4.43 (4.02 to 4.84)	—	—
5000 JAU	158	3.61 (3.26 to 3.96)	1.27 (0.78 to 1.77) 26.1% (16.7% to 34.7%)	<.001	2.98 (2.57 to 3.40)	1.45 (0.86 to 2.03) 32.7% (20.8% to 43.3%)	<.001
Second season (2016) (Linear model analysis [†])							
Placebo	155	5.48 (5.06 to 5.90)	—	—	5.28 (4.80 to 5.77)	—	—
5000 JAU	153	3.22 (2.80 to 3.65)	2.26 (1.66 to 2.85) 41.2% (31.9% to 49.7%)	<.001	3.24 (2.75 to 3.72)	2.05 (1.36 to 2.73) 38.7% (27.4% to 49.0%)	<.001
Third season (2017) (Linear model analysis [†])							
Placebo	145	5.36 (4.90 to 5.82)	—	—	4.59 (4.08 to 5.10)	—	—
5000 JAU	146	2.99 (2.53 to 3.45)	2.37 (1.72 to 3.02) 44.2% (33.9% to 53.6%)	<.001	2.93 (2.42 to 3.44)	1.66 (0.94 to 2.38) 36.2% (22.2% to 48.7%)	<.001

Bold type indicates statistically significant values.

vs, versus; TNSMS, total nasal symptom medication score; CI, confidence interval; JAU, Japanese allergy unit; Placebo, subjects received placebo throughout the 3-year study; 5000 JAU, subjects received 5000 Japanese allergy units (JAU) throughout the 3-year study. The Japanese cypress pollen dispersal period was tentatively defined as after the day the JCY pollen count exceeded 30 grains/cm²/day, a greater impact on symptoms caused by JCY pollen than JC pollen, because of the overlap between the JC pollen dispersal periods and JCY pollen dispersal periods (2015; March 27, 2016; March 28, 2017; April 13). [†]Dependent variable: TNSMs score. Fixed effect: treatment groups.

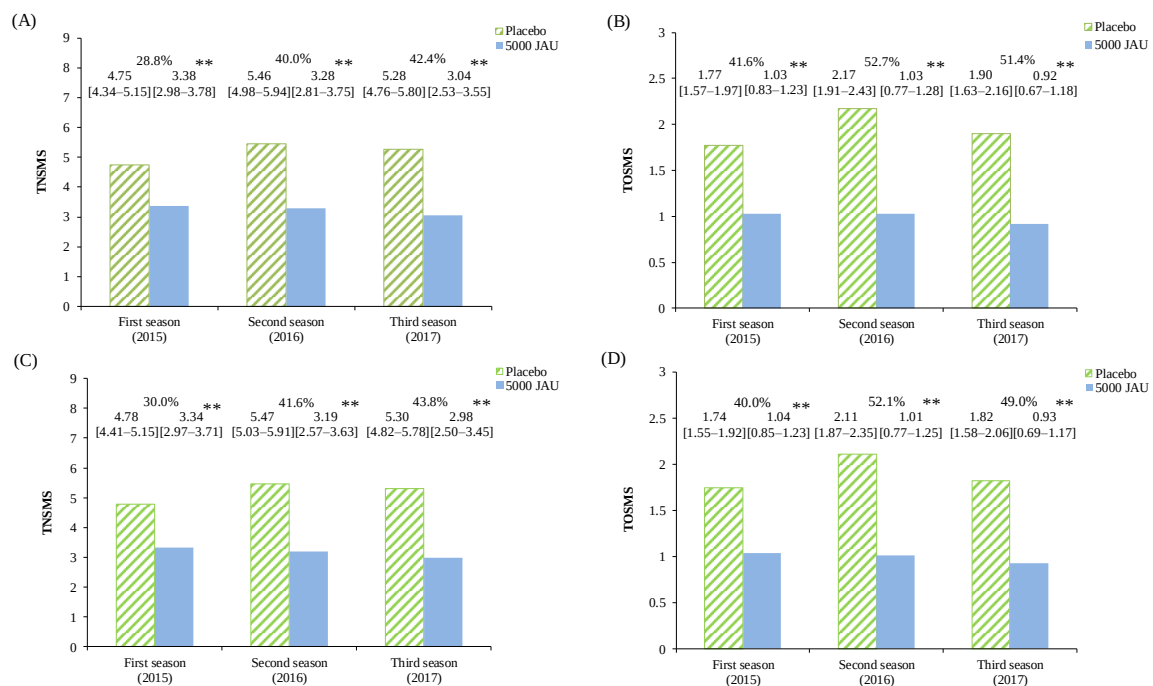
Supplementary Table 2.

Baseline demographic profile of patients

Characteristic	Placebo (N=159)	5000 JAU (N=158)
Sex, n (%)		
Male	71 (44.7%)	69 (43.7%)
Female	88 (55.3%)	89 (56.3%)
Age (y), mean $\pm$ SD	35.0 $\pm$ 14.4	34.3 $\pm$ 15.2
JC pollinosis duration (y)		
Mean $\pm$ SD	15.2 $\pm$ 9.0	16.6 $\pm$ 9.2
JC pollen-specific IgE (kUA/L), n (%)		
≥ 3.5 –<17.5	76 (47.8%)	63 (39.9%)
≥ 17.5 –<50	55 (34.6%)	61 (38.6%)
≥ 50 –<100	22 (13.8%)	23 (14.6%)
≥ 100	6 (3.8%)	11 (7.0%)
Mean $\pm$ SD	32.42 $\pm$ 44.50	43.30 $\pm$ 77.74
Sensitization status, n (%)		
JC pollen		
Monosensitized	20 (12.6%)	13 (8.2%)
Polysensitized	139 (87.4%)	145 (91.8%)
Cypress pollen- sensitized*	123 (77.4%)	126 (79.7%)
JCY pollen-specific IgE (kUA/L), n (%)		
<0.35	12 (7.5%)	11 (7.0%)
≥ 0.35 to <0.7	24 (15.1%)	21 (13.3%)
≥ 0.7 to <3.5	85 (53.5%)	69 (43.7%)
≥ 3.5 to <17.5	35 (22.0%)	52 (32.9%)
≥ 17.5 to <50	3 (1.9%)	5 (3.2%)

JC, Japanese cedar; IgE, immunoglobulin E; SD, standard deviation; JAU, Japanese allergy unit; Placebo, placebo throughout; 5000 JAU, 5000 JAU throughout; y, years; n, number.

* Cypress pollen sensitization was defined as a cypress pollen-specific IgE level of ≥ 0.70 kUA/L.



Supplementary Figure 1. Least squares means of total nasal symptom and medication score (TNSMS) and total ocular symptom and medication score (TOSMS) with 95% confidence intervals and relative differences (%) to the placebo group (Placebo) in Japanese cypress (JCY) specific immunoglobulin E positive (≥ 0.7 kUA/L) patients (A, B) and the inclusion of JCY-sIgE pseudo-positives (≥ 0.35 kUA/L) patients (C, D) during the Japanese cedar (JC) pollen and JCY pollen dispersal period in the first (February 11 to April 25 2015), second (February 13 to April 23 2016), and third (February 16 to April 26 2017) study seasons. JC and JCY pollen counts are indicated by green shading and orange striped shading, respectively. Placebo, subjects received placebo throughout the 3-year study; 5000 JAU, subjects received 5000 Japanese allergy units (JAU) throughout the 3-year study. The JC and JCY pollen counts in central Tokyo were measured using a Durham sampler. For JC pollen, the cumulative counts throughout the 3-year study (3892, 2994, and 2894 grains/cm², respectively) were in line with the count of the average year. JCY pollen counts throughout the 3-year study (815, 1221, and 1041 grains/cm², respectively) were also in line with the count of the average year. **p < 0.001 vs Placebo.