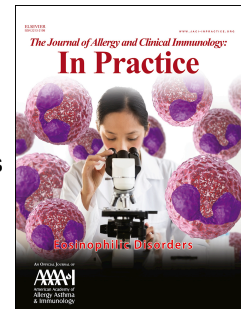


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Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets

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

Disclosure of potential conflict of interest

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Authors' contributions

SY, MG, KO, and YO contributed to the conduct of the study and data collection and interpretation. SK designed and operated the study. YM wrote the manuscript. All the listed authors were involved in the review and approved the final content.

Abstract <250 / max 250 words>

Background: Japanese cedar (JC) pollinosis is a common allergic rhinitis in Japan. JC pollen sublingual immunotherapy (SLIT) tablets are licensed for the treatment of JC pollinosis.

Objective: To assess the disease-modifying effects of JC pollen SLIT tablets over 5 years (2014–2019), comprising a 3-year treatment period and 2-year follow-up.

Methods: A total of 1042 patients with JC pollinosis (aged 5–64 years) were included in the study. An optimal dose-finding study was performed in the first 15 months, after which 240 patients in the placebo (P) group and 236 patients in the optimal active dose (A) group (5000 Japanese Allergy Units) were re-randomized to receive P or A for an additional 18 months (designated AA, AP, PA, and PP groups). Clinical efficacy was evaluated by the total nasal symptom and medication score (TNSMS) during the peak symptom period of each JC pollen season over 3 years of treatment and 2 years of observation after treatment cessation.

Results: The AA, AP, and PA groups exhibited significantly reduced TNSMS; however the largest relative reduction was seen in the AA group both during the treatment period (third season, 46.3% vs PP, $P < .001$) and during the 2-year follow-up period (fourth and fifth seasons, 45.3% and 34.0% vs PP, respectively; $P < .001$). The most common adverse drug reactions were mild reactions at the administration site.

Conclusions: JC pollen SLIT tablets show sustained clinical efficacy during 3 years of treatment and sustained disease-modifying effects for at least 2 years after treatment cessation.

What is already known about this topic?

Previous reports from this trial demonstrated that JC pollen SLIT provided sustained efficacy in a treatment duration-dependent manner; however, the magnitude and duration of disease modification after treatment cessation had not been evaluated. (33/35 words)

What does this article add to our knowledge?

Additional data from this 5-year study demonstrate that JC pollen SLIT administration for approximately 18 months also provides long-term benefits after treatment cessation, but that 3 years of treatment provides the more robust disease-modifying effect. (35/35 words)

75

76 How does this study impact current management guidelines?

77 More durable disease-modifying effects of JC pollen SLIT are obtained after 3 years compared with 18
78 months of continuous administration at an optimal dose. (24/35 words)

79

80 Key words: Allergy immunotherapy; Sublingual immunotherapy; Disease modification; Sustained efficacy;
81 Japanese cedar; Allergy; Allergic rhinitis; Conjunctivitis; Children

82

83

84 Abbreviations

85 AA group - Active-to-active (5000 re-randomized to 5000 JAU)

86 ADR - Adverse drug reaction

87 AE - Adverse event

88 AP group - Active-to-placebo (5000 JAU re-randomized to placebo)

89 JAU - Japanese allergy unit

90 JC - Japanese cedar

91 JCY - Japanese cypress

92 JRQLQ - Japanese Rhinoconjunctivitis Quality of Life Questionnaire

93 PA group - Placebo-to-active (placebo re-randomized to 5000 JAU)

94 PP group - Placebo-to-placebo (placebo re-randomized to placebo)

95 QOL - Quality of life

96 SLIT - Sublingual immunotherapy

97 TNSMS - Total nasal symptom and medication score

98 TOSMS - Total ocular symptom and medication score

99

Manuscript <max 3,500 words, current 4,020>

Introduction

Allergen immunotherapy is considered to be the only treatment that results in long-term remission of allergic symptoms and suppression of novel allergen sensitization through a disease-modifying effect.^{1,2,3,4,5} Sublingual immunotherapy (SLIT) tablets have been shown to have a disease-modifying effect in grass pollinosis and to improve the quality of life (QOL) of allergic patients while exhibiting a favorable safety profile.⁶

Japanese cedar (JC) pollinosis is the most common seasonal allergic rhinitis in Japan. Despite region-specific variations in timing of the JC pollen dispersal season, most patients suffer allergic symptoms between mid-February and late April. JC pollen SLIT tablets are currently approved for the treatment of JC pollinosis in Japan.

We have performed a 5-year study of the efficacy and safety of JC pollen SLIT tablets for the treatment of JC pollinosis. To date, we have reported on findings up to the third JC pollen dispersal season and shown that efficacy is treatment duration-dependent and is accompanied by a favorable safety profile.^{7,8} The study design comprised an optimal dose-finding period of 15 months that encompassed the first JC pollen dispersal season, and subjects in the optimal dose group (A group) and placebo group (P group) were then re-randomized into four groups: A→A (AA group), A→P (AP group), P→A (PA group), and P→P (PP group) prior to entering the second season. Treatment was concluded after the end of the third season. Follow-up efficacy and safety evaluations were continued for 2 years (fourth and fifth seasons) after the end of the 3-year treatment period. This innovative study design allows for comparison of efficacy and safety in patients receiving different treatment doses, different durations of administration of the optimal dose, and different durations of observation after treatment cessation. In the present study, we report complete safety and efficacy data acquired for the 2 years after the end of treatment cessation.

Methods

Trial design

This randomized, double-blind, placebo-controlled trial (JapicCTI-142579) complied with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the clinical review committee of each medical institution. Written consent was obtained from all subjects or, in the case of minor subjects, their legal representatives. The sponsor (Torii, Tokyo, Japan), subjects, legal representatives, investigators, and those involved in executing the study were blinded until the database was locked at the end of the fifth JC pollen dispersal season.

Details of the trial have been reported previously,^{7,8} and are available in this article's Online Repository. In brief, the trial included dose-finding, long-term treatment, and observational phases and encompassed the JC pollen dispersal seasons over 5 years (2015–2019) (Figure E1). Between August 2014 and November 2015, which encompassed the first JC pollen dispersal season, four cohorts of patients were administered SLIT containing 2000, 5000, or 10,000 Japanese Allergy Units (JAU) or placebo to determine the optimal drug dose. In November 2015, approximately 3 months before the start of the second JC pollen dispersal season, patients in the optimal dose group (5000 JAU) and the placebo group were re-randomized at a ratio of 2:1:1:2 to AA:AP:PA:PP groups and were administered P or A until the end of the third JC pollen dispersal season (end of April 2017). The duration of continuous treatment with active drug was 33 months for the AA group, 15 months for the AP group, and 18 months for the PA group. Safety and efficacy observations were continued during the fourth and fifth seasons and the trial concluded in May 2019.

Study drug

The study drug was a fast-dissolving lyophilized SLIT tablet manufactured by ALK-Abelló (Hørsholm, Denmark). The common unit for JC pollen SLIT products in Japan is JAU, and 12.5 µg/mL of Cry j 1, the major allergen of JC pollen, was defined as 10,000 JAU/mL by the Japanese Society of Allergology Task Force in 1996.⁹ JC SLIT tablets with strengths of 2000, 5000 and 10,000 JAU each have a Cry j 1 content corresponding to the stated potency as calculated with the 10,000 JAU/mL of the JC pollen standard extracts. Subjects were administered one tablet daily, which was held sublingually for 1 min before swallowing. Oral antihistamines, eye drops, and nasal vasoconstrictors were provided to the subjects as rescue medications and

were to be used only when intolerable symptoms developed. Details are available in this article's Online Repository.

Trial population

Subject enrollment was restricted to residents of Tokyo and its suburbs to minimize variations in natural exposure to JC pollen. Inclusion criteria have been previously reported^{7,8} and are available in this article's Online Repository.

Outcomes

JC pollen counts were recorded in central Tokyo using the Durham method. Nasal and eye symptom evaluation was based on the Japanese guidelines for allergic rhinitis 2017¹⁰ and on previous experience with the clinical development of JC pollen SLIT drops.¹¹ As previously reported,⁷ the primary endpoint was the Total Nasal Symptom and Medication Score (TNSMS). The major secondary endpoints were the Total Ocular Symptom and Medication Score (TOSMS), well days, severe symptom days, proportion of participants who did not use rescue medication, cumulative frequency of rescue medication use, and QOL assessment by the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ).^{10,12} Details are available in this article's Online Repository. Safety was evaluated by monitoring adverse events (AEs), including adverse drug reactions (ADRs, defined as study drug-related AEs), starting with the first study drug administration. Serum levels of JC pollen-specific IgE and IgG4 were measured by ImmunoCAP (SRL, Tokyo, Japan).

Statistical analysis

The basis for the sample size was described previously.⁷ In brief, the sample size for the dose-finding study was based on the results of the clinical trial of JC pollen SLIT drops¹¹ and was set at a minimum of 230 patients/group to allow for withdrawal during the treatment period. The primary endpoint after determining the optimal dose was TNSMS during the peak symptom period in the fifth season (2019). In the primary analysis, we applied mixed-model repeated measures (MMRM). Paired comparisons were performed between four groups based on the least squares (LS) mean; a closed testing procedure was performed to

adjust for multiplicity in the primary analysis following a sequential order: AA vs PP, PA vs PP, AP vs PP, AA vs AP, AA vs PA. The primary evaluation set was the full analysis set (FAS) and included participants whose TNSMS during the peak symptom period in 2015 had been measured at least once (FAS-2019). The same analyses were applied to the analysis of symptoms, medications, and combined scores in the peak symptom period and JC pollen dispersal season for all seasons, i.e., 2016 to 2019, after re-randomization in the same population (FAS-2019). Fieller's theorem was used for calculating the confidence interval for the rate of decrease in the LS mean.¹³ Details of the statistical analyses, including the secondary endpoints, are available in this article's Online Repository. All statistical tests were performed using SAS software version 9.3 or higher (SAS Institute, Cary, NC, USA) with a 5% significance level. All tests and 95% confidence intervals were two-sided.

Results

Participants

Participant disposition is shown in Figure E2. Consent was obtained from 1256 patients, of whom 1042 patients were randomized into four groups for the initial dose-finding period. After establishing 5000 JAU as the optimal dose, a total of 476 patients from the P and A (5000 JAU) groups were re-randomized for the long-term treatment period (PP: 159, PA: 81, AP: 78, AA: 158). Of those 476 patients, 438 completed the long-term treatment period to April 30, 2017 (PP: 145, PA: 75, AP: 73, AA: 145), and 412 of those patients completed the 5-year trial (PP: 138, PA: 69, AP: 68, AA: 137). The reasons for withdrawal and the withdrawal rate were similar among all treatment groups at the completion of the long-term treatment period (PP: 8.8%, PA: 7.4%, AP: 6.4%, AA: 8.2%) and at the completion of the observational period (PP: 4.8%, PA: 8.0%, AP: 6.8%, AA: 5.5%). The key clinicopathological and demographic characteristics of the four re-randomized treatment groups are shown in Table E1 and did not differ significantly. Further details are provided in previous reports.^{7,8}

JC pollen counts during the evaluation periods

Figure E3 shows the cumulative pollen counts during the JC and Japanese cypress (JCY) pollen dispersal seasons from 2015 to 2019. JCY pollen levels were extremely high in the fourth season (2018). In that year, JCY pollen dispersal began 1 week earlier than usual and was followed by dispersal of a very large amount of pollen over a short period. Because this JCY dispersal pattern was unprecedented, the peak symptom period for the 2018 season was shortened to March 25th, the day before the start of the large-scale dispersal of JCY pollen, rather than March 29th to March 31st for the remaining years (Figure 1A and 1C). This was defined prior to unblinding the data and was introduced to reduce the effect of the abnormal JCY pollen count and dispersal period, considering the high homology of JC and JCY pollen allergens.^{14,15} Table E2 shows the JC pollen counts and dates of the JC pollen dispersal seasons and peak symptom periods for each year. The JC pollen dispersal seasons encompassed the JCY pollen dispersal periods (April).

Efficacy

The TNSMS for the full analysis set (FAS-2019) analyzed by MMRM are shown for the peak symptom period in Table 1A and for the JC pollen dispersal season in Table E3A. The average daily TNSMS in the fourth and fifth seasons for the FAS-2019 are shown in Figure 1A and 1B.

The LS mean TNSMS for the AA group was significantly different from that of the PP group during the peak symptom periods of all years ($P < .001$). The rate of TNSMS decrease in the AA group varied between 32.1% (first season) and 46.3% (third season) and remained high even in the fifth season (34.0%). For the PA group, the rate of TNSMS decrease was also significantly different from that of the PP group in the second season (31.6%) through the fifth season (26.3%), with the largest change occurring in the third season (38.5%). The TNSMS for the AP group was significantly lower than that of the PP group in all seasons except the fifth. The TNSMS for the AA group was significantly lower than that of the AP group in the fourth and fifth seasons. The rate of TNSMS decrease was not significantly different between the PA and AA groups in either the fourth or fifth seasons. Furthermore, for the fourth season (2018), when a large amount of JCY pollen was dispersed, the TNSMS for the peak symptom period from March 20 to March 31 was calculated without considering the amount of JCY pollen dispersed, that is, using the original definition (before the statistical analysis plan amendment). The differences between TNSMS in the PP and AP versus AA groups

were similar to those observed for the peak symptom period which was shortened to end on March 25 (Table E4). As shown in Table E3A, similar results were observed when the TNSMSs were evaluated for each JC pollen dispersal season.

The TOSMS for the FAS-2019 are shown for the peak symptom period in Table IB and for the JC pollen dispersal season in Table E3B. The average daily TOSMS in the fourth and fifth seasons for the FAS-2019 are shown in Figure 1C and 1D.

All active treatment groups (AP, PA, AA) showed significantly lower TOSMSs compared with the PP group in the peak symptom periods of the second through fifth seasons. TOSMS in the AA group in the third through fifth seasons were significantly lower than those for the AP group but did not differ significantly from those for the PA group during the same period. Analysis of TOSMS in the JC pollen dispersal seasons identified no significant differences between the AP and PP groups in the fourth and fifth seasons (Table E3B). The differences between TOSMS in the PP versus AA and PA groups during the JC pollen dispersal seasons were similar to those observed in the peak symptom period of each year.

Table II shows the analysis of symptom relief during the peak symptom periods of each year. The analysis included the proportion of patients with well days, severe symptom days, and rescue medication use.

The AA and PA groups showed significantly more well days and fewer severe symptom days compared with the PP group in the second through fifth seasons. The AP group also showed significant improvements in well days and severe symptom days compared with the PP group in the second and third seasons. A significantly higher proportion of subjects in the AA group compared with the PP group did not use rescue medications in the second through fifth seasons (Table II). A significantly higher proportion of the PA and AP groups compared with the PP group did not use rescue medications in the second through fourth and second and third seasons, respectively.

The analyses of symptom relief during the JC pollen dispersal seasons of each year for the FAS-2019 are shown in Table E5.

Table E6 shows the cumulative frequency of rescue medication use for each JC pollen dispersal season. Rescue medication use was significantly lower for the AA group versus the PP group for the second through fifth seasons, for the PA group versus the PP group for the third and fourth seasons, and for the AP group versus the PP group for the second through fourth seasons.

Table III shows the JRQLQ general state scores recorded on March 31 of each year as well as the individual component scores (Table E7) recorded in the fourth and fifth seasons. The evaluations in the first through third seasons have been previously reported.⁸ The AA and PA groups showed significant improvements in JRQLQ general state compared with the PP group in the fourth and fifth seasons, whereas no significant improvements were seen for the AP group. For the individual JRQLQ components, significant improvements were observed in the AA group compared with the PP group in the fourth and fifth seasons, but no changes were noted for the AP group in the fourth and fifth seasons (Table E7). Significant improvements were observed in the PA group compared with the PP group for four of the six components (except “social functioning” and “physical problems”) in the fourth season, and in five of the six components (except “social functioning”) in the fifth season.

The JRQLQ evaluations performed on March 15 were similar to those recorded on March 31 (Table E8).

Immunological responses

Figure 2 shows the changes in serum JC pollen-specific IgE and IgG4 levels for each group throughout the study. Increases in serum JC pollen-specific IgE (Figure 2A) were observed immediately after initiation of active dosing in the AA, AP, and PA groups, which peaked at 1-3 months and then declined. Although the AA group received active drug for 33 months, serum JC pollen-specific IgE levels gradually decreased and returned to baseline levels by the end of the treatment period (after the third season). The changes during the 2-year observational period were similar for all groups.

Serum JC pollen-specific IgG4 (Figure 2B) levels also increased in the AA, AP, and PA groups immediately after initiation of active drug administration, and high levels were subsequently maintained during both the long-term treatment and observational periods.

Safety

Evaluation of AEs and ADRs during the long-term treatment period are shown in Table IV. The safety analysis for these groups during the dose-finding period has been previously reported.⁷ No deaths occurred, and there were no serious ADRs, including anaphylactic shock, severe systemic allergic reactions, or AEs requiring epinephrine administration or hospitalization, during the long-term treatment or observational

periods. Most AEs and ADRs were mild. The ADR profile in the PA group was similar to that observed in the 5000 JAU group during the dose-finding period, and most ADRs were oral allergic reactions (data not shown). Compared with the safety analysis of the dose-finding period, no new safety issues arose during the long-term treatment and observational periods.

Discussion

We report here the results of the first 5-year, randomized, parallel-group, placebo-controlled, double-blind trial of JC pollen SLIT tablets in which patients were administered active drug for between 15 and 33 months and then followed up for an additional 2-year observational period.

Evaluating the efficacy of treatment for pollinosis is not easy because the amount of dispersed pollen and climatic conditions vary from year to year and consequently constant exposure conditions cannot be maintained. In the present study under natural pollen exposure, the cumulative JC pollen counts varied from 2894 to 5016 grains/cm² over 5 years. We previously reported that JC pollen SLIT drops (2000 JAU) group had significantly lower TNSMS compared with placebo group (7.04 vs. 8.61; $p < .0001$, -18% in 2011, 6537 grains/cm²) in the first season with a large amount of JC pollen dispersal.¹¹ In the present study, we found that the 2000 JAU JC pollen SLIT tablets group also showed similar improvements in TNSMS compared with the placebo group (5.49 vs. 6.98; $p < .001$, -21.4% in 2015, 3893 grains/cm²) in the first season (dose-finding period).⁷ Based on these data, the TNSMS in the peak symptom period of the placebo group varied corresponding to the amount of JC pollen dispersed; however, this finding suggests that the relative difference of TNSMS to the placebo group can be used to evaluate the therapeutic effect of JC pollen SLIT products without being affected by various conditions of JC pollen dispersal.

The optimal dose of 5000 JAU was identified in the initial 15-month dose-finding period, after which patients in the placebo and 5000 JAU groups were re-randomized to P or A groups for the long-term treatment period of 18 months. Thus, this study allowed us to independently compare efficacy according to the duration of the treatment period and the duration of the post-treatment cessation observation period.

Our results showing treatment duration-dependent effects on TNSMS during the long-term treatment period validates our findings in the previous report from this trial.⁷ Of note, in the present study, we observed

>30% improvements in TNSMS in the AP and PA groups, both of which had 15–18 months of treatment but with different timing of administration. Furthermore, the improvements in both groups continued for 2–2.5 years after treatment cessation, despite high season-to-season variability in pollen exposure, thus confirming the reproducibility of the disease-modifying effect in the AP and PA groups. These findings support the primary conclusion from this 5-year study; namely, that the efficacy of JC pollen SLIT tablets is only modestly influenced by the time at which treatment is initiated and completed.

TNSMS in the peak symptom period, which was the primary endpoint, was well controlled across all 5 seasons, as demonstrated by the AA group, which received 33 months of treatment and showed a clinically relevant sustained efficacy of 34.0% in the fifth season. This value exceeds the minimum clinically relevant effect required by the World Allergy Organization (>20% improvement vs placebo)¹⁶ and the US Food and Drug Administration ($\geq 15\%$ improvement vs placebo with $\leq 10\%$ upper limit for 95% CI).^{17,18,19} Only the AA group showed significant improvements compared with the PP group in all secondary endpoints during the peak symptom periods through the fifth season, and this was true for both the peak symptom period and the JC pollen dispersal season.

We previously reported that the beneficial effects observed in the AP group were continued for 15 months after treatment cessation,^{7,8} and the present study extends those findings to report significant improvements in TNSMS and TOSMS for 27 months after treatment cessation in the AP group compared with the PP group (22.3% and 29.4%, respectively, at the start of the fourth season). At 39 months after treatment cessation (prior to the start of pollen dispersal in the fifth season), the AP group showed significant improvement compared with the PP group only in TOSMS. Thus, the efficacy obtained after 15 months of 5000 JAU administration, which encompassed only the first JC pollen season, was sustained for the next three JC pollen seasons and then diminished thereafter.

The TNSMS improvements in the AA group exceeded the improvements in the PA group in the third season (AA 46.3% and PA 38.5%) and fifth season (AA 34.0% and PA 26.3%), which corresponded to the end of the long-term treatment period and observation period, respectively. In the PA group, improvements in some JRQLQ individual component scores had diminished by the fourth season, and improvements in rescue medication use and cumulative frequency of rescue medication use were no longer evident in the fifth season. Thus, longer treatment (33 months vs 18 months) with 5000 JAU was superior both for efficacy

during treatment and for sustained disease modification after treatment cessation, and the disease modification of the longer treatment expected to last beyond the next three seasons compare to that in the AP group (33 months vs 15 months).

Scadding et al.²⁰ examined the sustained effects of 2 years of SLIT for grass-pollen-induced allergic rhinitis by nasal allergen challenge at 3 years (1 year after treatment cessation) and they found no significant difference between SLIT and placebo in improving the nasal response to allergen challenge. In our study, we observed sustained efficacy in the AP and PA groups, both of which had similar durations of treatment (15 months and 18 months, respectively) to that of Scadding et al. This discrepancy may have been due to differences in the methods of assessment, which was nasal allergen challenge in the study by Scadding et al. and self-reported symptom records after natural pollen exposure in the present study. Furthermore, unlike our trial design, the study of Scadding et al. was not designed to compare 2 vs 3 years of SLIT. We could compare 1.5 (15 months and 18 months) and 3 years (33 months) of SLIT in the same 5-year study under natural pollen exposure, allowing us to conclude that approximately 1.5 years treatment of SLIT tablets yielded long-term benefits for next three seasons after treatment cessation, and 3 years treatment of SLIT tablets showed the more robust disease-modifying effect after treatment cessation.

In the present study, increases in serum JC pollen-specific IgE were detected early after the start of active drug administration, but the IgE response shifted toward IgG4 upon continued drug administration, especially in the AA group (33-month treatment period). Moreover, like the observed clinical improvements, these immunologic changes were sustained for 2 years after treatment cessation, which is entirely consistent with a long-term disease-modifying mechanism. For the placebo group, there were small seasonal variations in the JC pollen-specific IgE and IgG4 levels during each JC pollen seasons throughout the study. All active treatment groups also showed small seasonal variations in the levels of both JC pollen-specific IgE and IgG4. In the AA group, the seasonal increase in IgE tended to be smaller but that in IgG4 tended to be larger than those in the placebo group. These results are similar to those obtained in a 3-year treatment/2-year follow-up study in which the disease-modifying effects of SQ-standardized grass SLIT tablets were investigated,^{6,21} and suggest that SLIT induces immunomodulation and/or subsequent clinical tolerance.

The relatively mild AEs observed and favorable long-term safety profile of JC pollen SLIT tablets observed in the present study support their long-term use in real-world clinical practice. The main weakness

of this study was that we were limited to a 2-year follow-up period because of the trial design. Further reports from real-world clinical practice will undoubtedly indicate whether the beneficial disease-modifying effects of 3 years of JC pollen SLIT will persist beyond 2 years after treatment cessation.

In conclusion, we have demonstrated the dose-dependent efficacy of JC pollen SLIT tablets for JC pollinosis and shown that the improvement in clinical efficacy and immunological response persists after treatment cessation in a treatment duration-dependent manner. These results strongly suggest that treatment with JC pollen SLIT tablets for at least 3 years will provide both long-term efficacy and disease-modifying effects.

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Figure Legends

Figure 1.

Daily averaged TNSMS (A, B) and TOSMS (C, D) in the fourth (A, C) and fifth (B, D) JC pollen seasons for the full analysis set (FAS-2019). JC and JCY pollen counts are indicated by gray and striped shading, respectively.

Figure 2.

Serum levels of JC pollen-specific IgE (A) and JC pollen-specific IgG4 (B) for the full analysis set (FAS-2019). The JC pollen dispersal seasons (indicated by black boxes) started at approximately 6, 18, 30, 42, and 54 months, respectively, after initiation of study drug administration. Data are presented as means $\pm$ 95% CIs.

1 **Table I. Analysis of rhinitis (TNSMS) and conjunctivitis (TOSMS) scores in the peak symptom period for the full analysis set (FAS-**
2 **2019)**
3 **(A) TNSMS**

Treatment group	N	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI)	P value	Absolute difference vs AP group (95% CI)	P value	Absolute difference vs PA group (95% CI)	P value
			Relative difference vs PP group (95% CI)		Relative difference vs AP group (95% CI)		Relative difference vs PA group (95% CI)	
<i>First season (2015) (Linear); Dose-finding period *</i>								
Placebo (PP and PA)	257	6.98 (6.57 to 7.40)	—	—	—	—	—	—
5000 JAU (AA and AP)	255	4.74 (4.32 to 5.16)	2.24 (1.65 to 2.83) 32.1% (24.6% to 39.1%)	<.001	—	—	—	—
<i>Second season (2016) (MMRM); Long-term treatment period</i>								
PP	159	6.94 (6.25 to 7.64)	—	—	—	—	—	—
AP	78	4.38 (3.79 to 4.98)	2.56 (1.65 to 3.47) 36.9% (25.5% to 46.9%)	<.001	—	—	—	—
PA	81	4.75 (3.99 to 5.50)	2.20 (1.17 to 3.22) 31.6% (18.1% to 43.8%)	<.001	−0.36 (−1.33 to 0.60) −8.3% (−33.3% to 12.6%)	.458	—	—
AA	158	3.82 (3.42 to 4.21)	3.13 (2.33 to 3.93) 45.1% (36.6% to 52.5%)	<.001	0.57 (−0.15 to 1.29) 13.0% (−3.8% to 26.4%)	.120	0.93 (0.08 to 1.79) 19.6% (2.0% to 33.1%)	.032
<i>Third season (2017) (MMRM); Long-term treatment period</i>								
PP	159	6.57 (5.89 to 7.26)	—	—	—	—	—	—
AP	78	4.16 (3.59 to 4.73)	2.41 (1.52 to 3.30) 36.7% (25.0% to 47.0%)	<.001	—	—	—	—
PA	81	4.04 (3.28 to 4.81)	2.53 (1.50 to 3.56) 38.5% (24.5% to 51.2%)	<.001	0.12 (−0.84 to 1.08) 2.9% (−22.0% to 24.0%)	.805	—	—
AA	158	3.53 (3.07 to 4.00)	3.04 (2.21 to 3.87) 46.3% (36.6% to 54.8%)	<.001	0.63 (−0.11 to 1.37) 15.1% (−2.8% to 29.9%)	.094	0.51 (−0.39 to 1.41) 12.6% (−11.4% to 30.1%)	.264

Fourth season (2018) (MMRM); Observational period

PP	159	7.31 (6.61 to 8.01)	—	—	—	—	—	—
AP	78	5.68 (4.80 to 6.56)	1.63 (0.51 to 2.76) 22.3% (7.4% to 35.8%)	.005	—	—	—	—
PA	81	4.88 (4.04 to 5.72)	2.43 (1.34 to 3.53) 33.3% (19.5% to 45.8%)	<.001	0.80 (−0.42 to 2.02) 14.1% (−8.2% to 32.2%)	.197	—	—
AA	158	4.00 (3.47 to 4.53)	3.31 (2.43 to 4.19) 45.3% (35.8% to 53.7%)	<.001	1.68 (0.65 to 2.70) 29.5% (13.2% to 42.4%)	.001	0.88 (−0.11 to 1.87) 18.0% (−2.7% to 33.7%)	.083

Fifth season (2019) (MMRM); Observational period

PP	159	7.71 (6.88 to 8.55)	—	—	—	—	—	—
AP	78	6.55 (5.55 to 7.56)	1.16 (−0.15 to 2.46) 15.0% (−2.0% to 30.1%)	.083	—	—	—	—
PA	81	5.69 (4.78 to 6.59)	2.03 (0.80 to 3.26) 26.3% (11.2% to 39.7%)	.001	0.87 (−0.48 to 2.22) 13.3% (−8.3% to 30.6%)	.208	—	—
AA	158	5.09 (4.47 to 5.71)	2.62 (1.58 to 3.66) 34.0% (22.4% to 44.1%)	<.001	1.47 (0.28 to 2.65) 22.4% (5.0% to 36.0%)	.015	0.60 (−0.50 to 1.69) 10.5% (−10.1% to 26.5%)	.285

Bold type indicates statistically significant values.

vs, versus; *TNSMS*, total nasal symptom medication score; *CI*, confidence interval; *JAU*, Japanese allergy unit; *MMRM*, mixed model for repeated measures; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

* Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

9 (B) TOSMS

Treatment group	N	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI) Relative difference vs PP group (95% CI)	P value	Absolute difference vs AP group (95% CI) Relative difference vs AP group (95% CI)	P value	Absolute difference vs PA group (95% CI) Relative difference vs PA group (95% CI)	P value
<i>First season (2015) (Linear); Dose-finding period *</i>								
Placebo (PP and PA)	257	2.68 (2.47 to 2.89)	–	–	–	–	–	–
5000 JAU (AA and AP)	255	1.57 (1.36 to 1.78)	1.11 (0.81 to 1.41) 41.4% (31.8% to 50.2%)	<.001	–	–	–	–
<i>Second season (2016) (MMRM); Long-term treatment period</i>								
PP	159	3.00 (2.62 to 3.39)	–	–	–	–	–	–
AP	78	1.56 (1.23 to 1.89)	1.44 (0.93 to 1.95) 48.0% (34.1% to 60.1%)	<.001	–	–	–	–
PA	81	1.75 (1.37 to 2.14)	1.25 (0.70 to 1.79) 41.6% (25.7% to 55.6%)	<.001	–0.19 (–0.70 to 0.31) –12.2% (–52.7% to 17.8%)	.458	–	–
AA	158	1.22 (1.00 to 1.44)	1.78 (1.34 to 2.23) 59.3% (49.6% to 67.7%)	<.001	0.34 (–0.05 to 0.74) 21.8% (–4.2% to 40.6%)	.091	0.53 (0.09 to 0.97) 30.4% (6.5% to 47.3%)	.018
<i>Third season (2017) (MMRM); Long-term treatment period</i>								
PP	159	2.49 (2.14 to 2.84)	–	–	–	–	–	–
AP	78	1.49 (1.14 to 1.84)	1.00 (0.50 to 1.50) 40.1% (22.3% to 55.5%)	<.001	–	–	–	–
PA	81	1.37 (0.99 to 1.75)	1.12 (0.60 to 1.64) 44.9% (26.4% to 61.1%)	<.001	0.12 (–0.40 to 0.64) 8.0% (–32.1% to 37.4%)	.651	–	–
AA	158	1.06 (0.85 to 1.28)	1.43 (1.02 to 1.84) 57.3% (45.9% to 67.0%)	<.001	0.43 (0.02 to 0.84) 28.7% (1.6% to 47.5%)	.041	0.31 (–0.13 to 0.74) 22.5% (–12.1% to 44.3%)	.164
<i>Fourth season (2018) (MMRM); Observational period</i>								
PP	159	3.23 (2.84 to 3.62)	–	–	–	–	–	–
AP	78	2.28 (1.79 to 2.77)	0.95 (0.32 to 1.58) 29.4% (10.9% to 45.8%)	.003	–	–	–	–

PA	81	1.79 (1.37 to 2.22)	1.44 (0.86 to 2.01) 44.5% (28.8% to 58.4%)	<.001	0.49 (−0.16 to 1.13) 21.3% (−8.3% to 43.4%)	.140	—	—
AA	158	1.44 (1.16 to 1.73)	1.79 (1.30 to 2.27) 55.3% (44.3% to 65.0%)	<.001	0.84 (0.27 to 1.40) 36.7% (14.7% to 52.7%)	.004	0.35 (−0.16 to 0.86) 19.6% (−10.8% to 40.6%)	.175
<i>Fifth season (2019) (MMRM); Observational period</i>								
PP	159	3.33 (2.90 to 3.76)	—	—	—	—	—	—
AP	78	2.58 (2.04 to 3.12)	0.75 (0.06 to 1.44) 22.5% (2.0% to 40.4%)	.033	—	—	—	—
PA	81	2.16 (1.67 to 2.64)	1.17 (0.52 to 1.82) 35.2% (17.2% to 51.0%)	<.001	0.42 (−0.30 to 1.15) 16.4% (−13.9% to 39.1%)	.253	—	—
AA	158	1.80 (1.48 to 2.13)	1.53 (0.99 to 2.06) 45.9% (32.9% to 57.0%)	<.001	0.78 (0.15 to 1.41) 30.1% (7.1% to 46.8%)	.015	0.36 (−0.23 to 0.94) 16.5% (−13.0% to 37.0%)	.232

10 Bold type indicates statistically significant values.

11 vs, versus; *TOSMS*, total ocular symptom medication score; *CI*, confidence interval; *JAU*, Japanese allergy unit; *MMRM*, mixed model for
 12 repeated measures; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

13 * Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

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1 Table II. Symptom relief evaluation during the peak symptom periods for the full analysis set (FAS-2019)

Treatment group	N	Probability (%) * (95% CI)	vs PP		vs AP		vs PA	
			Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value
<i>Well days [†] (Generalized linear [‡])</i>								
<i>First season (2015); Dose-finding period [§]</i>								
Placebo	257	21.3 (17.6 to 25.6)	—	—	—	—	—	—
5000 JAU	255	33.5 (29.4 to 37.8)	1.86 (1.37 to 2.51)	<.001	—	—	—	—
<i>Second season (2016); Long-term treatment period</i>								
PP	155	23.4 (18.5 to 29.1)	—	—	—	—	—	—
AP	76	40.5 (32.3 to 49.3)	2.23 (1.41 to 3.55)	<.001	—	—	—	—
PA	79	45.2 (36.5 to 54.1)	2.70 (1.70 to 4.30)	<.001	1.21 (0.73 to 2.00)	.461	—	—
AA	153	50.2 (44.4 to 55.9)	3.30 (2.27 to 4.81)	<.001	1.48 (0.97 to 2.26)	.071	1.22 (0.80 to 1.87)	.354
<i>Third season (2017); Long-term treatment period</i>								
PP	145	30.0 (24.5 to 36.3)	—	—	—	—	—	—
AP	73	43.4 (34.8 to 52.4)	1.79 (1.13 to 2.83)	.013	—	—	—	—
PA	75	55.0 (45.9 to 63.8)	2.85 (1.79 to 4.52)	<.001	1.59 (0.95 to 2.67)	.077	—	—
AA	146	57.4 (51.3 to 63.2)	3.14 (2.16 to 4.56)	<.001	1.76 (1.13 to 2.72)	.012	1.10 (0.71 to 1.71)	.664
<i>Fourth season (2018); Observational period</i>								
PP	144	24.6 (19.7 to 30.3)	—	—	—	—	—	—
AP	71	34.4 (26.2 to 43.8)	1.61 (0.99 to 2.62)	.056	—	—	—	—
PA	72	44.9 (36.5 to 53.7)	2.50 (1.59 to 3.93)	<.001	1.55 (0.92 to 2.63)	.100	—	—
AA	140	51.5 (45.3 to 57.7)	3.26 (2.22 to 4.77)	<.001	2.02 (1.27 to 3.23)	.003	1.30 (0.85 to 2.00)	.230
<i>Fifth season (2019); Observational period</i>								
PP	139	25.3 (19.9 to 31.6)	-	-				
AP	69	26.3 (19.0 to 35.3)	1.05 (0.62 to 1.78)	.845				
PA	70	37.8 (29.3 to 47.0)	1.79 (1.10 to 2.92)	.020	1.70 (0.96 to 3.00)	.068	-	-
AA	138	41.3 (34.9 to 48.1)	2.08 (1.37 to 3.14)	<.001	1.97 (1.19 to 3.27)	.008	1.16 (0.73 to 1.86)	.531
<i>Severe symptom days [¶] (Generalized linear [‡])</i>								
<i>First season (2015); Dose-finding period [§]</i>								
Placebo	257	33.6 (29.2 to 38.3)	—	—	—	—	—	—

5000 JAU	255	13.3 (10.6 to 16.5)	0.30 (0.22 to 0.42)	<.001	—	—	—	—
<i>Second season (2016); Long-term treatment period</i>								
PP	155	37.1 (31.1 to 43.4)	—	—	—	—	—	—
AP	76	16.2 (10.9 to 23.4)	0.33 (0.19 to 0.56)	<.001	—	—	—	—
PA	79	15.3 (10.4 to 22.0)	0.31 (0.18 to 0.52)	<.001	0.93 (0.49 to 1.77)	.836	—	—
AA	153	9.5 (6.5 to 13.6)	0.18 (0.11 to 0.29)	<.001	0.54 (0.29 to 1.00)	.049	0.58 (0.32 to 1.06)	.075
<i>Third season (2017); Long-term treatment period</i>								
PP	145	31.0 (25.2 to 37.4)	—	—	—	—	—	—
AP	73	14.8 (9.6 to 22.0)	0.39 (0.22 to 0.68)	<.001	—	—	—	—
PA	75	10.4 (6.3 to 16.9)	0.26 (0.14 to 0.49)	<.001	0.67 (0.32 to 1.41)	.295	—	—
AA	146	7.7 (4.8 to 12.0)	0.19 (0.10 to 0.33)	<.001	0.48 (0.24 to 0.96)	.039	0.71 (0.34 to 1.50)	.375
<i>Fourth season (2018); Observational period</i>								
PP	144	38.9 (32.6 to 45.5)	—	—	—	—	—	—
AP	71	28.8 (21.3 to 37.7)	0.64 (0.39 to 1.03)	.067	—	—	—	—
PA	72	16.8 (11.3 to 24.4)	0.32 (0.19 to 0.55)	<.001	0.50 (0.27 to 0.93)	.028	—	—
AA	140	13.3 (9.4 to 18.5)	0.24 (0.15 to 0.39)	<.001	0.38 (0.22 to 0.66)	<.001	0.76 (0.41 to 1.39)	.367
<i>Fifth season (2019); Observational period</i>								
PP	139	38.0 (31.4 to 45.1)	—	—	—	—	—	—
AP	69	31.3 (23.2 to 40.6)	0.74 (0.45 to 1.22)	.243	—	—	—	—
PA	70	25.5 (17.9 to 34.9)	0.56 (0.33 to 0.95)	.033	0.75 (0.41 to 1.38)	.358	—	—
AA	138	21.0 (16.0 to 27.1)	0.43 (0.28 to 0.68)	<.001	0.58 (0.35 to 0.99)	.046	0.78 (0.44 to 1.36)	.378
<i>Proportion of participants who did not use rescue medication (Logistic regression **)</i>								
<i>First season (2015); Dose-finding period [§]</i>								
Placebo	257	47.9 (41.8 to 54.0)	—	—	—	—	—	—
5000 JAU	255	69.8 (63.9 to 75.1)	2.52 (1.75 to 3.62)	<.001	—	—	—	—
<i>Second season (2016); Long-term treatment period</i>								
PP	155	49.7 (41.9 to 57.5)	—	—	—	—	—	—
AP	76	76.3 (65.5 to 84.5)	3.26 (1.76 to 6.04)	<.001	—	—	—	—
PA	79	67.1 (56.0 to 76.5)	2.06 (1.17 to 3.63)	.012	0.63 (0.31 to 1.28)	.204	—	—
AA	153	73.2 (65.6 to 79.6)	2.77 (1.72 to 4.46)	<.001	0.85 (0.45 to 1.61)	.612	1.34 (0.74 to 2.42)	.331
<i>Third season (2017); Long-term treatment period</i>								
PP	145	53.8 (45.6 to 61.7)	—	—	—	—	—	—

AP	73	71.2 (59.9 to 80.4)	2.13 (1.16 to 3.89)	.014	–	–	–	–
PA	75	78.7 (68.0 to 86.5)	3.17 (1.67 to 6.02)	<.001	1.49 (0.70 to 3.15)	.298	–	–
AA	146	83.6 (76.6 to 88.7)	4.37 (2.53 to 7.54)	<.001	2.05 (1.05 to 4.01)	.035	1.38 (0.68 to 2.79)	.372
<i>Fourth season (2018); Observational period</i>								
PP	144	47.2 (39.2 to 55.4)	–	–	–	–	–	–
AP	71	57.7 (46.0 to 68.6)	1.53 (0.86 to 2.71)	.148	–	–	–	–
PA	72	69.4 (57.9 to 79.0)	2.54 (1.40 to 4.62)	.002	1.66 (0.84 to 3.31)	.147	–	–
AA	140	74.3 (66.4 to 80.8)	3.23 (1.96 to 5.33)	<.001	2.11 (1.15 to 3.87)	.015	1.27 (0.68 to 2.38)	.454
<i>Fifth season (2019); Observational period</i>								
PP	139	46.8 (38.6 to 55.1)	–	–	–	–	–	–
AP	69	55.1 (43.3 to 66.3)	1.40 (0.78 to 2.49)	.260	–	–	–	–
PA	70	55.7 (44.0 to 66.8)	1.43 (0.80 to 2.55)	.223	1.03 (0.53 to 2.00)	.939	–	–
AA	138	68.8 (60.6 to 76.0)	2.51 (1.54 to 4.11)	<.001	1.80 (0.99 to 3.27)	.053	1.76 (0.97 to 3.18)	.063

Bold type indicates statistically significant values.

vs, versus; *CI*, confidence interval; *JAU*, Japanese allergy unit; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

* Probability was calculated as [total number of well days or severe symptom days] / ([number of participants] × number of days during the peak symptom period)], and was estimated based on a generalized linear model. For participants who did not use rescue medication, the probability was estimated based on a logistic regression model.

** Fixed effect: treatment groups.

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

‡ Generalized linear models using a logit link function, assuming exchangeable (compound symmetry) covariance structure within subjects,

12 with treatment group as a fixed effect.

13 § Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

14 ¶ Days with at least one symptom evaluated as 4+ for nasal symptoms or 3+ for ocular symptoms.

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Table III. JRQLQ general state evaluated on March 31 in the fourth and fifth seasons for the full analysis set (FAS-2019)

Evaluation index	n (%)				P value (Wilcoxon rank-sum test vs PP group)		
	PP	AP	PA	AA	AP	PA	AA
<i>Fourth season</i>							
N	138	68	69	131			
0 (Fine)	1 (0.7)	1 (1.5)	2 (2.9)	5 (3.8)	.207	<.001	<.001
1	18 (13.1)	11 (16.2)	15 (21.7)	31 (23.8)			
2	27 (19.7)	14 (20.6)	26 (37.7)	40 (30.8)			
3	54 (39.4)	30 (44.1)	16 (23.2)	39 (30.0)			
4 (Crying)	37 (27.0)	12 (17.6)	10 (14.5)	15 (11.5)			
Missing data	1	0	0	1			
<i>Fifth season</i>							
N	134	67	67	131			
0 (Fine)	3 (2.3)	2 (3.0)	4 (6.0)	8 (6.2)	.647	.023	<.001
1	25 (18.8)	14 (20.9)	10 (14.9)	40 (30.8)			
2	32 (24.1)	15 (22.4)	30 (44.8)	38 (29.2)			
3	53 (39.8)	28 (41.8)	19 (28.4)	32 (24.6)			
4 (Crying)	20 (15.0)	8 (11.9)	4 (6.0)	12 (9.2)			
Missing data	1	0	0	1			

JRQLQ, Japanese Rhinoconjunctivitis Quality of Life Questionnaire; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout; vs, versus.

Table IV. Evaluation of safety in the re-randomized treatment groups

Complete trial period										
	PP (N = 159)		AP (N = 78)		PA (N = 81)		AA (N = 158)		Total (N = 476)	
	n	%	n	%	n	%	n	%	n	%
Serious AE	10	6.3	6	7.7	5	6.2	7	4.4	28	5.9
Serious ADR	—	—	—	—	—	—	—	—	—	—
All AEs	144	90.6	71	91.0	76	93.8	147	93.0	438	92.0
Mild	142	89.3	71	91.0	76	93.8	146	92.4	435	91.4
Moderate	20	12.6	11	14.1	15	18.5	29	18.4	75	15.8
Severe	1	0.6	2	2.6	—	—	1	0.6	4	0.8
All ADRs	34	21.4	33	42.3	25	30.9	82	51.9	174	36.6
Mild	34	21.4	33	42.3	25	30.9	81	51.3	173	36.3
Moderate	—	—	—	—	—	—	1	0.6	1	0.2
Severe	—	—	—	—	—	—	—	—	—	—
Long-term treatment period										
	PP (N = 159)		AP (N = 78)		PA (N = 81)		AA (N = 158)		Total (N = 476)	
	n	%	n	%	n	%	n	%	n	%
Serious AE	3	1.9	3	3.8	—	—	4	2.5	10	2.1
Serious ADR	—	—	—	—	—	—	—	—	—	—
All AEs	119	74.8	58	74.4	64	79.0	120	75.9	361	75.8
Mild	117	73.6	55	70.5	63	77.8	118	74.7	353	74.2
Moderate	10	6.3	8	10.3	3	3.7	9	5.7	30	6.3
Severe	—	—	1	1.3	—	—	1	0.6	2	0.4
All ADRs	7	4.4	—	—	16	19.8	10	6.3	33	6.9
Mild	7	4.4	—	—	16	19.8	10	6.3	33	6.9
Moderate	—	—	—	—	—	—	—	—	—	—
Severe	—	—	—	—	—	—	—	—	—	—
Observation period										
	PP (N = 145)		AP (N = 73)		PA (N = 75)		AA (N = 145)		Total (N = 438)	
	n	%	n	%	n	%	n	%	n	%
Serious AE	4	2.8	2	2.7	3	4.0	3	2.1	12	2.7
Serious ADR	—	—	—	—	—	—	—	—	—	—
All AEs	105	72.4	46	63.0	55	73.3	115	79.3	321	73.3
Mild	99	68.3	46	63.0	55	73.3	112	77.2	312	71.2
Moderate	11	7.6	3	4.1	3	4.0	14	9.7	31	7.1
Severe	—	—	1	1.4	—	—	—	—	1	0.2
All ADRs	—	—	—	—	—	—	—	—	—	—

AE, adverse event; ADR, adverse drug reaction; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout.

Fig. 1A

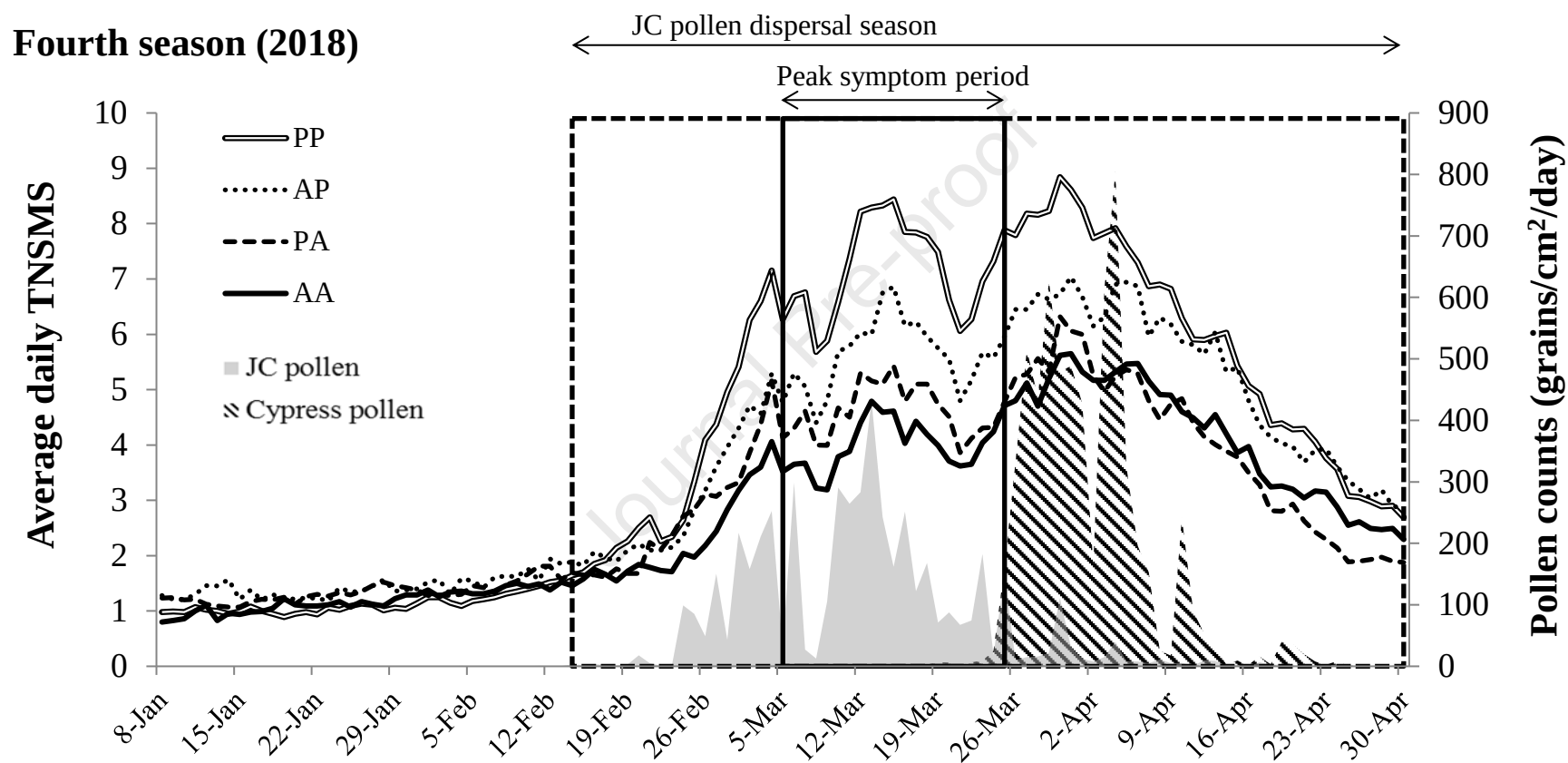


Fig. 1B

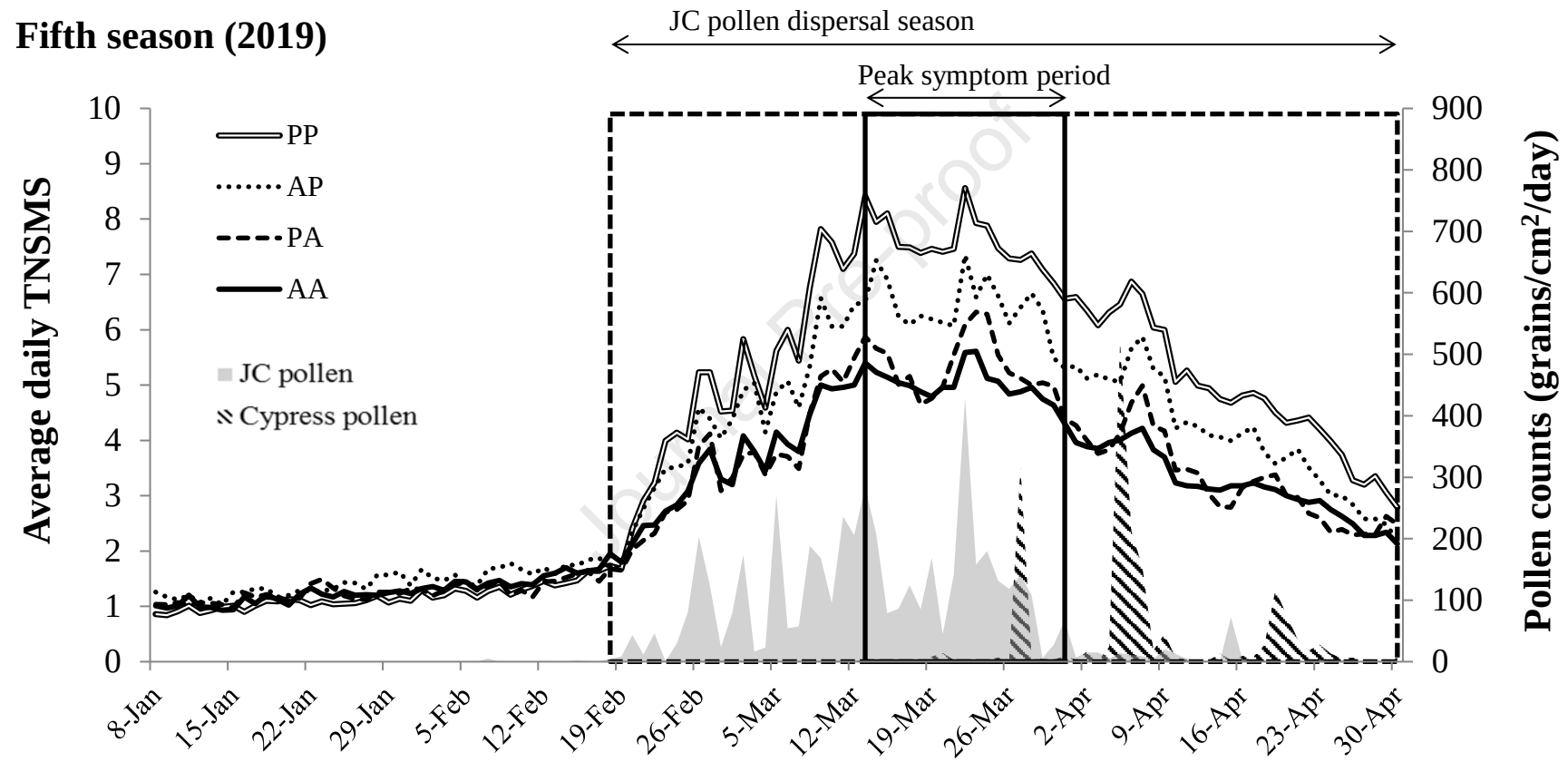


Fig. 1C

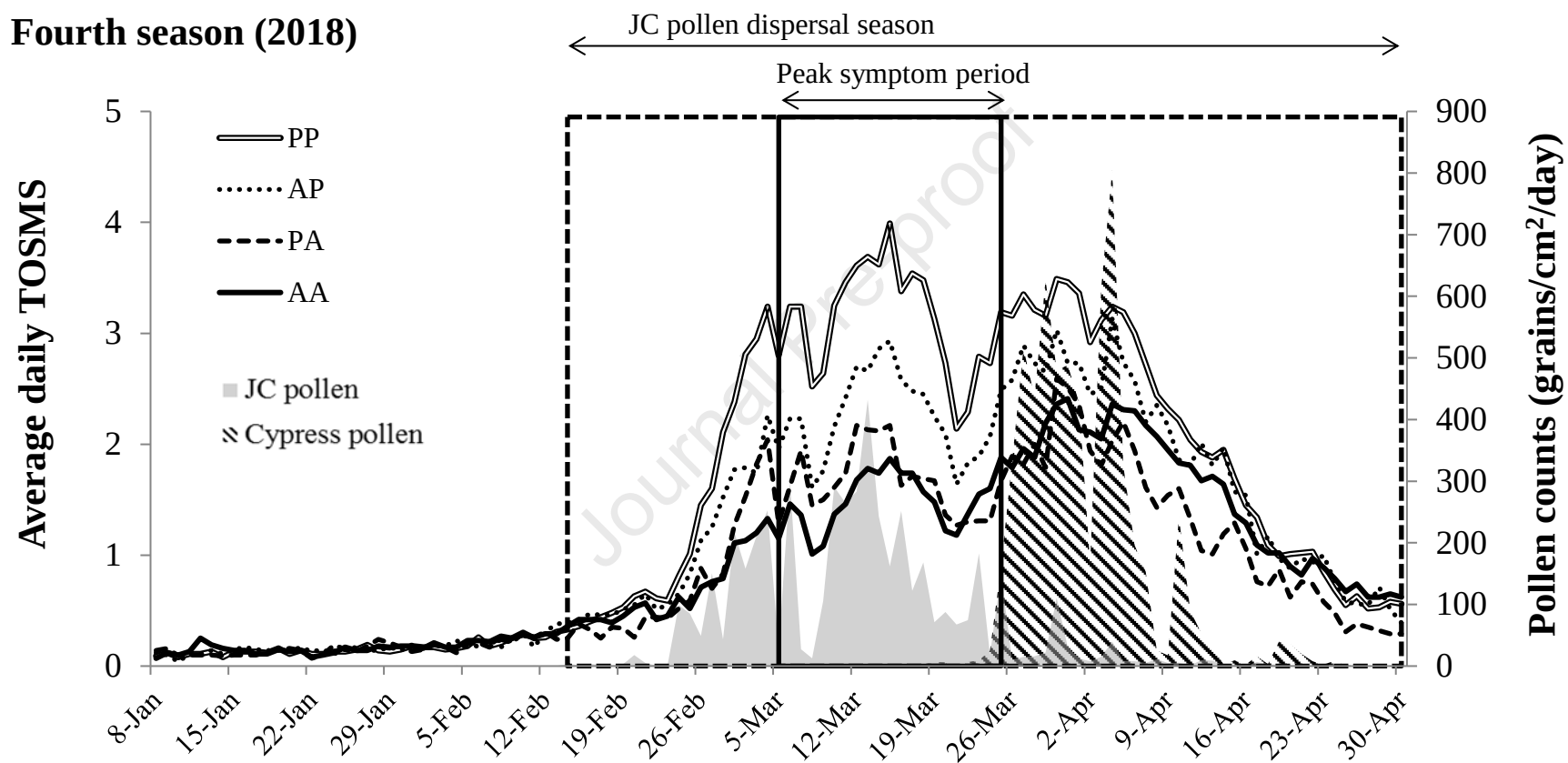
Fourth season (2018)

Fig. 1D

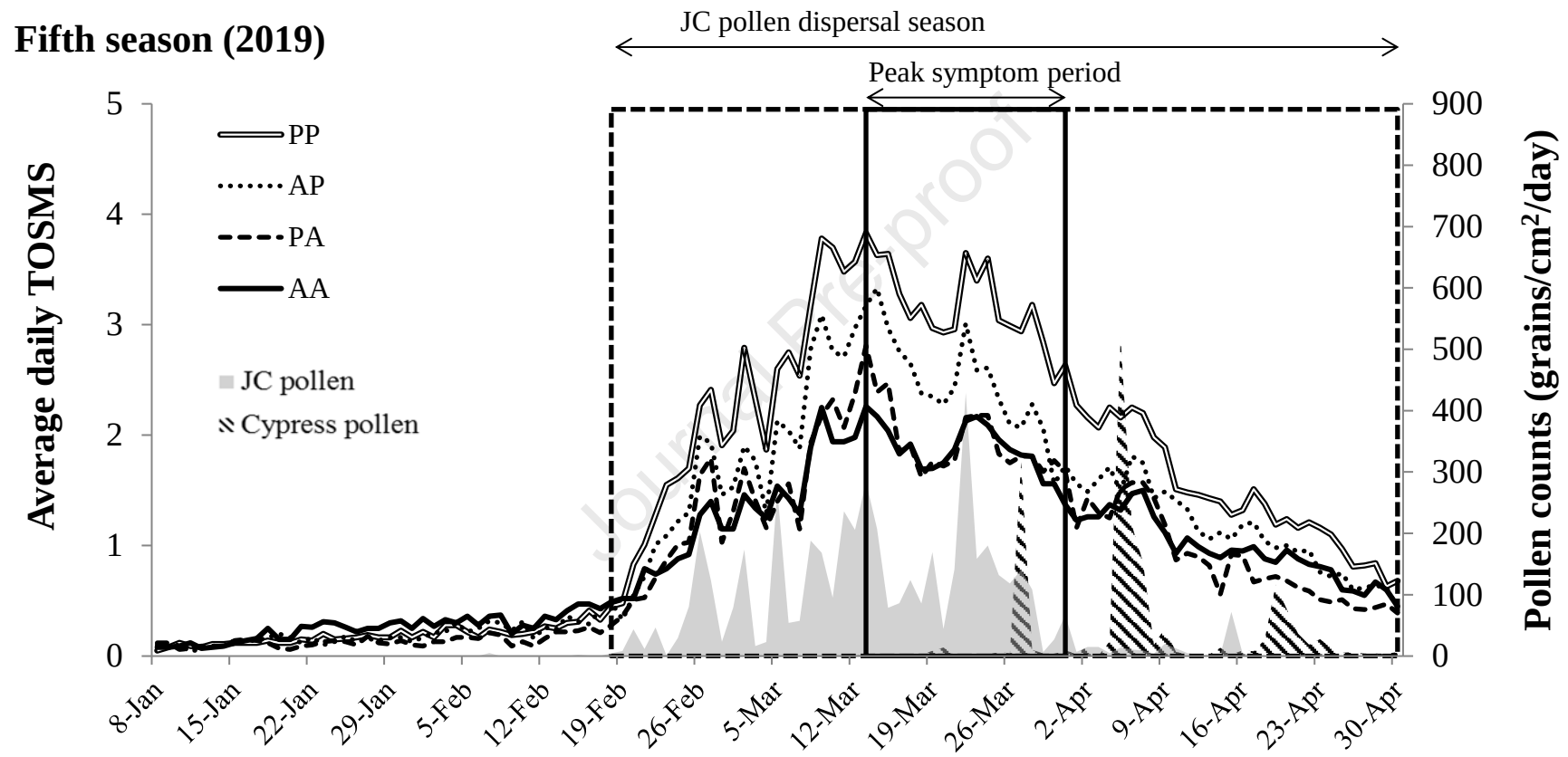


Fig 2A

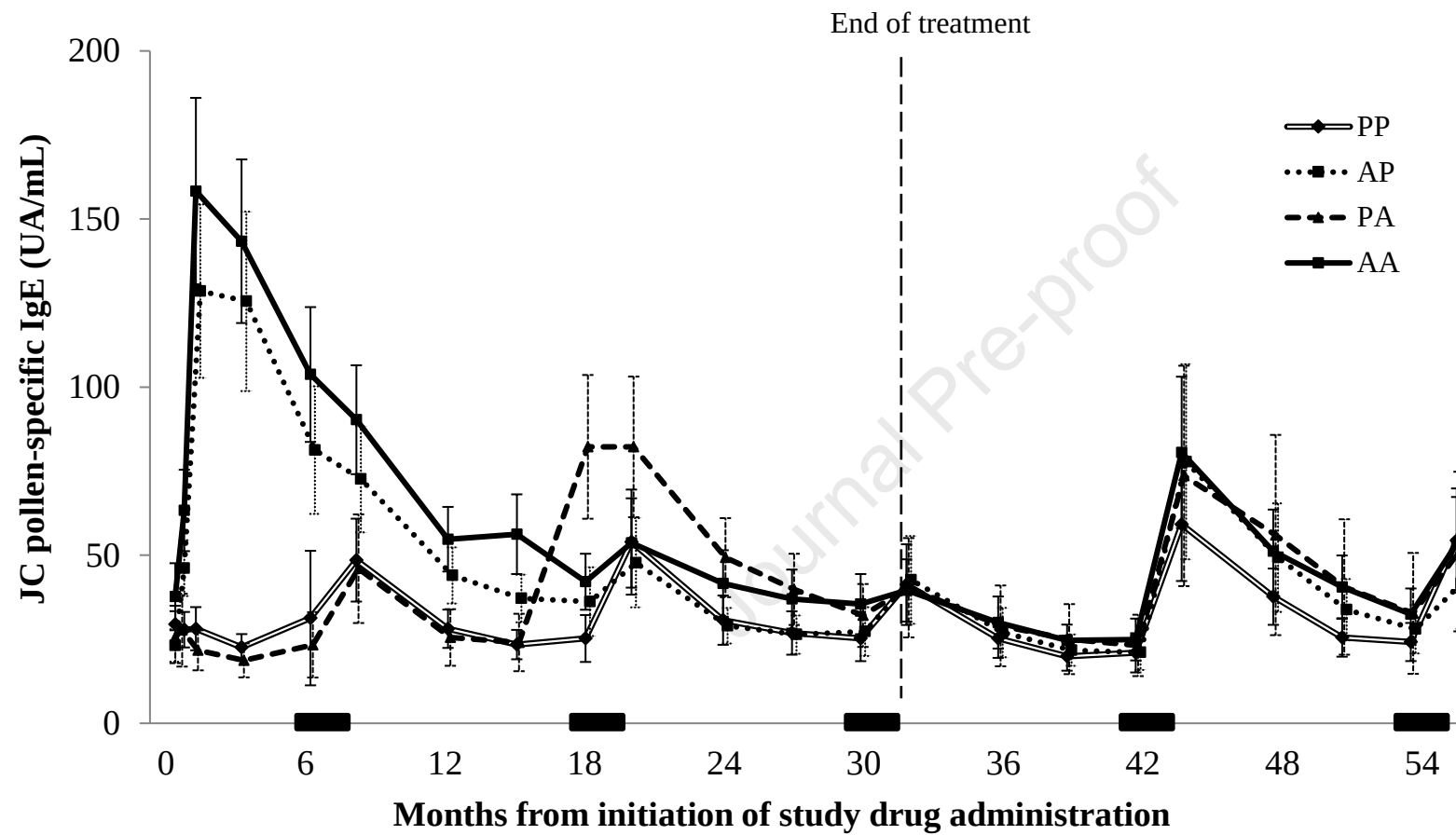


Fig 2B

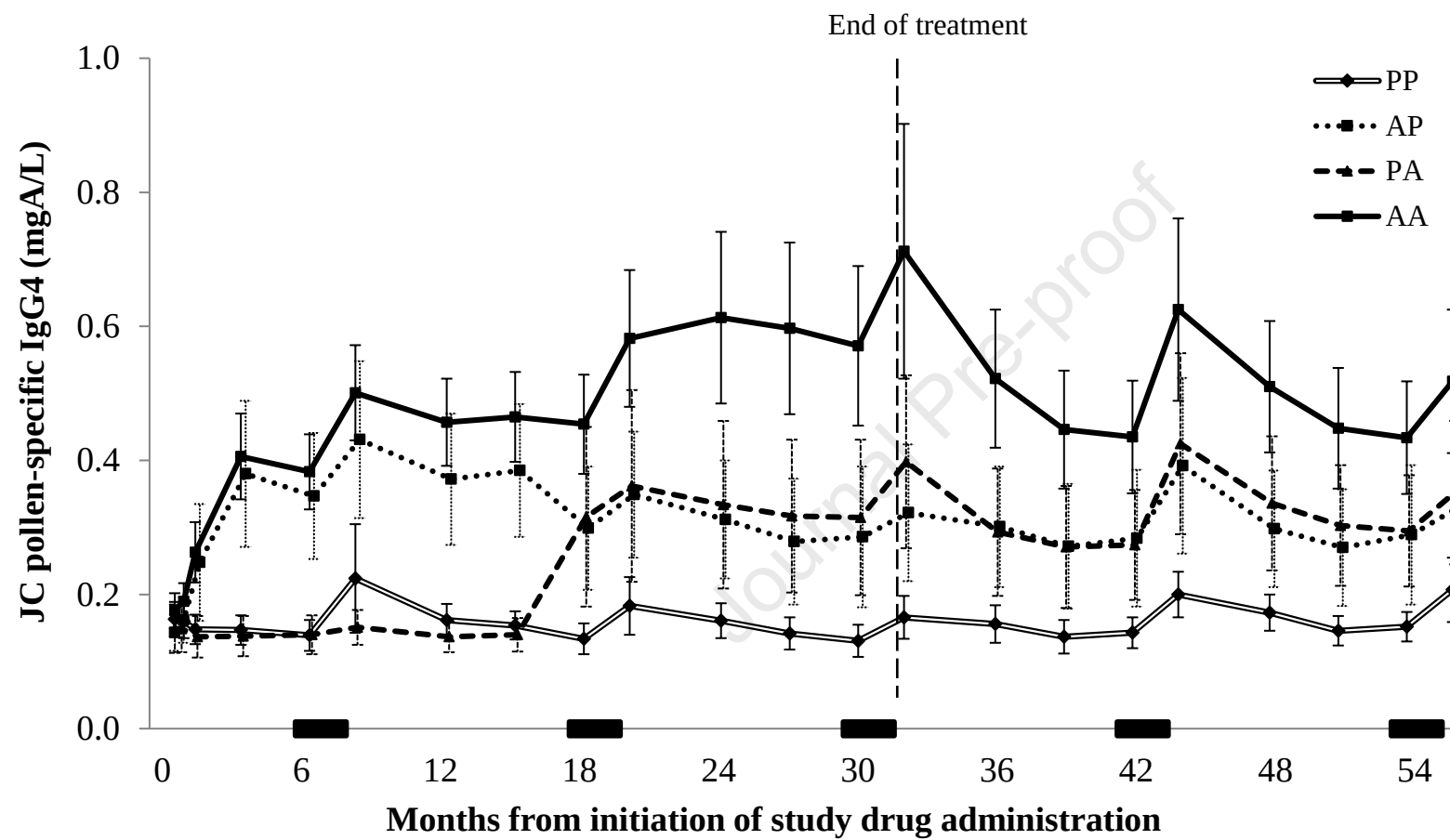


Table E1. Baseline clinicopathological characteristics of patients in the re-randomized groups

Characteristic	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), n (%)					
5–11	21 (13.2%)	12 (15.4%)	11 (13.6%)	23 (14.6%)	67 (14.1%)
12–17	8 (5.0%)	2 (2.6%)	5 (6.2%)	8 (5.1%)	23 (4.8%)
18–64	130 (81.8%)	64 (82.1%)	65 (80.2%)	127 (80.4%)	386 (81.1%)
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
JC pollinosis duration (y)					
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%)
Mean $\pm$ SD	32.42 $\pm$ 44.50	25.99 $\pm$ 26.88	29.70 $\pm$ 41.22	43.30 $\pm$ 77.74	34.52 $\pm$ 55.70
Sensitization status, n (%)					
JC pollen					
Monosensitized	20 (12.6%)	11 (14.1%)	8 (9.9%)	13 (8.2%)	52 (10.9%)
Polysensitized	139 (87.4%)	67 (85.9%)	73 (90.1%)	145 (91.8%)	424 (89.1%)
Cypress pollen- sensitized*	123 (77.4%)	57 (73.1%)	65 (80.2%)	126 (79.7%)	371 (77.9%)

JC, Japanese cedar; IgE, immunoglobulin E; SD, standard deviation; JAU, Japanese allergy unit; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout.

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

Table E2. JC pollen counts during each evaluation period

Year	JC pollen dispersal season		Peak symptom period	
	Duration	JC pollen counts (grains/cm ²)	Duration	JC pollen counts (grains/cm ²)
2015	February 11 to April 25	3889	March 15 to March 31	1537
2016	February 13 to April 23	2985	March 9 to March 29	1569
2017	February 16 to April 26	2888	March 11 to March 31	1359
2018	February 14 to April 30	5012	March 5 to March 25	3343
2019	February 18 to April 30	4946	March 13 to March 31	2588

JC, Japanese cedar.

1 **Table E3. Analysis of rhinitis (TNSMS) and conjunctivitis (TOSMS) scores in the JC pollen dispersal season for the full analysis set**
2 **(FAS-2019)**
3 **(A) TNSMS**

Treatment group	N	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI) Relative difference vs PP group (95% CI)	P value	Absolute difference vs AP group (95% CI) Relative difference vs AP group (95% CI)	P value	Absolute difference vs PA group (95% CI) Relative difference vs PA group (95% CI)	P value
<i>First season (2015) (Linear); Dose-finding period *</i>								
Placebo (PP and PA)	257	4.74 (4.46 to 5.02)	—	—	—	—	—	—
5000 JAU (AA and AP)	255	3.53 (3.25 to 3.82)	1.21 (0.81 to 1.61) 25.5% (17.7% to 32.7%)	<.001	—	—	—	—
<i>Second season (2016) (MMRM); Long-term treatment period</i>								
PP	159	5.36 (4.83 to 5.88)	—	—	—	—	—	—
AP	78	3.75 (3.29 to 4.21)	1.60 (0.91 to 2.30) 29.9% (18.2% to 40.3%)	<.001	—	—	—	—
PA	81	3.86 (3.24 to 4.48)	1.50 (0.69 to 2.31) 28.0% (13.7% to 40.9%)	<.001	−0.10 (−0.87 to 0.67) −2.8% (−25.2% to 16.6%)	.791	—	—
AA	158	3.21 (2.90 to 3.51)	2.15 (1.54 to 2.76) 40.1% (31.4% to 47.8%)	<.001	0.55 (−0.00 to 1.10) 14.6% (−0.0% to 26.6%)	.051	0.65 (−0.04 to 1.34) 16.9% (−1.1% to 30.5%)	.065
<i>Third season (2017) (MMRM); Long-term treatment period</i>								
PP	159	5.26 (4.69 to 5.82)	—	—	—	—	—	—
AP	78	3.45 (2.99 to 3.92)	1.80 (1.07 to 2.53) 34.3% (22.2% to 44.9%)	<.001	—	—	—	—
PA	81	3.33 (2.73 to 3.94)	1.92 (1.10 to 2.74) 36.6% (22.4% to 49.2%)	<.001	0.12 (−0.64 to 0.88) 3.5% (−20.2% to 23.6%)	.758	—	—
AA	158	2.99 (2.61 to 3.36)	2.27 (1.59 to 2.94) 43.2% (33.1% to 51.9%)	<.001	0.47 (−0.13 to 1.06) 13.6% (−4.1% to 28.0%)	.123	0.35 (−0.36 to 1.06) 10.5% (−12.7% to 27.6%)	.334

<i>Fourth season (2018) (MMRM); Observational period</i>								
PP	159	5.70 (5.14 to 6.26)	—	—	—	—	—	—
AP	78	4.76 (4.05 to 5.48)	0.94 (0.03 to 1.84) 16.5% (0.7% to 30.7%)	.042	—	—	—	—
PA	81	3.99 (3.37 to 4.62)	1.71 (0.87 to 2.55) 30.0% (16.3% to 42.3%)	<.001	0.77 (−0.18 to 1.72) 16.2% (−4.1% to 32.7%)	.111	—	—
AA	158	3.61 (3.17 to 4.06)	2.09 (1.37 to 2.80) 36.6% (26.0% to 46.0%)	<.001	1.15 (0.31 to 1.99) 24.1% (7.5% to 37.3%)	.007	0.38 (−0.39 to 1.15) 9.5% (−11.1% to 25.6%)	.333
<i>Fifth season (2019) (MMRM); Observational period</i>								
PP	159	5.72 (5.08 to 6.35)	—	—	—	—	—	—
AP	78	4.84 (4.10 to 5.57)	0.88 (−0.09 to 1.85) 15.4% (−1.6% to 30.3%)	.074	—	—	—	—
PA	81	4.22 (3.52 to 4.91)	1.50 (0.56 to 2.44) 26.3% (10.6% to 40.1%)	.002	0.62 (−0.39 to 1.63) 12.8% (−9.0% to 30.6%)	.227	—	—
AA	158	3.83 (3.37 to 4.30)	1.88 (1.10 to 2.67) 33.0% (21.0% to 43.2%)	<.001	1.00 (0.14 to 1.87) 20.8% (3.3% to 34.5%)	.023	0.38 (−0.45 to 1.22) 9.1% (−12.4% to 25.5%)	.368

Bold type indicates statistically significant values.

vs, versus; *TNSMS*, total nasal symptom medication score; *CI*, confidence interval; *JAU*, Japanese allergy unit; *MMRM*, mixed model for repeated measures; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

* Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

9 (B) TOSMS

Treatment group	N	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI) Relative difference vs PP group (95% CI)	P value	Absolute difference vs AP group (95% CI) Relative difference vs AP group (95% CI)	P value	Absolute difference vs PA group (95% CI) Relative difference vs PA group (95% CI)	P value
<i>First season (2015) (Linear); Dose-finding period *</i>								
Placebo (PP and PA)	257	1.67 (1.53 to 1.81)	–	–	–	–	–	–
5000 JAU (AA and AP)	255	1.08 (0.94 to 1.22)	0.59 (0.40 to 0.78) 35.3% (25.0% to 44.7%)	<.001	–	–	–	–
<i>Second season (2016) (MMRM); Long-term treatment period</i>								
PP	159	2.06 (1.78 to 2.34)	–	–	–	–	–	–
AP	78	1.28 (0.99 to 1.57)	0.78 (0.37 to 1.18) 37.8% (20.0% to 53.2%)	<.001	–	–	–	–
PA	81	1.30 (1.00 to 1.59)	0.77 (0.36 to 1.17) 37.2% (19.3% to 52.7%)	<.001	–0.01 (–0.42 to 0.40) –1.0% (–39.9% to 27.0%)	.949	–	–
AA	158	0.98 (0.82 to 1.14)	1.08 (0.76 to 1.41) 52.5% (41.4% to 61.8%)	<.001	0.30 (–0.03 to 0.63) 23.6% (–2.6% to 41.7%)	.072	0.32 (–0.02 to 0.65) 24.4% (–1.4% to 42.2%)	.061
<i>Third season (2017) (MMRM); Long-term treatment period</i>								
PP	159	1.79 (1.53 to 2.06)	–	–	–	–	–	–
AP	78	1.14 (0.87 to 1.42)	0.65 (0.27 to 1.04) 36.3% (16.6% to 53.1%)	<.001	–	–	–	–
PA	81	1.08 (0.77 to 1.38)	0.72 (0.31 to 1.12) 39.9% (19.0% to 58.1%)	<.001	0.06 (–0.35 to 0.48) 5.7% (–36.7% to 36.5%)	.757	–	–
AA	158	0.90 (0.74 to 1.07)	0.89 (0.57 to 1.21) 49.6% (36.3% to 60.7%)	<.001	0.24 (–0.08 to 0.56) 20.9% (–9.2% to 41.3%)	.147	0.17 (–0.18 to 0.52) 16.1% (–21.9% to 39.4%)	.331
<i>Fourth season (2018) (MMRM); Observational period</i>								
PP	159	2.18 (1.90 to 2.47)	–	–	–	–	–	–
AP	78	1.72 (1.34 to 2.10)	0.46 (–0.01 to 0.93) 21.1% (–0.6% to 40.1%)	.056	–	–	–	–

PA	81	1.33 (1.05 to 1.61)	0.85 (0.45 to 1.25) 38.9% (22.6% to 53.2%)	<.001	0.39 (−0.08 to 0.86) 22.6% (−5.9% to 43.1%)	.107	—	—
AA	158	1.27 (1.04 to 1.50)	0.91 (0.55 to 1.27) 41.7% (27.7% to 53.8%)	<.001	0.45 (0.01 to 0.89) 26.1% (0.5% to 44.2%)	.047	0.06 (−0.30 to 0.42) 4.6% (−27.2% to 27.5%)	.740
<i>Fifth season (2019) (MMRM); Observational period</i>								
PP	159	2.24 (1.93 to 2.55)	—	—	—	—	—	—
AP	78	1.76 (1.36 to 2.17)	0.48 (−0.03 to 0.99) 21.3% (−1.6% to 41.1%)	.068	—	—	—	—
PA	81	1.45 (1.11 to 1.80)	0.79 (0.32 to 1.25) 35.2% (15.9% to 52.0%)	<.001	0.31 (−0.22 to 0.85) 17.7% (−15.2% to 41.4%)	.251	—	—
AA	158	1.26 (1.03 to 1.49)	0.98 (0.60 to 1.37) 43.9% (29.8% to 55.7%)	<.001	0.51 (0.04 to 0.97) 28.7% (2.9% to 46.5%)	.034	0.19 (−0.22 to 0.61) 13.4% (−19.0% to 35.4%)	.359

10 Bold type indicates statistically significant values.

11 vs, versus; *TOSMS*, total ocular symptom medication score; *CI*, confidence interval; *JAU*, Japanese allergy unit, *MMRM*, mixed model for
 12 repeated measures; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

13 * Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

14

Table E4. Analysis of rhinitis (TNSMS) and conjunctivitis (TOSMS) scores during the peak symptom period in the fourth season (2018) for the full analysis set (FAS-2019) without consideration of the large-amount dispersal of JCY pollen (March 20 to March 31 in 2018)

Treatment group	N	Least squares mean (95% CI)	Absolute difference vs PP group (95% CI) Relative difference vs PP group (95% CI)	P value	Absolute difference vs AP group (95% CI) Relative difference vs AP group (95% CI)	P value	Absolute difference vs PA group (95% CI) Relative difference vs PA group (95% CI)	P value
TNSMS Fourth season (2018) (MMRM); Observational period								
PP	159	7.72 (6.99 to 8.45)	—	—	—	—	—	—
AP	78	6.10 (5.13 to 7.06)	1.63 (0.42 to 2.84) 21.1% (5.8% to 34.9%)	.009	—	—	—	—
PA	81	5.23 (4.35 to 6.11)	2.50 (1.35 to 3.64) 32.3% (18.6% to 44.8%)	<.001	0.87 (−0.44 to 2.17) 14.3% (−8.0% to 32.2%)	.191	—	—
AA	158	4.60 (4.03 to 5.17)	3.12 (2.19 to 4.05) 40.4% (30.6% to 49.2%)	<.001	1.49 (0.37 to 2.61) 24.5% (7.2% to 38.0%)	.009	0.63 (−0.42 to 1.67) 12.0% (−9.4% to 28.2%)	.241
TOSMS Fourth season (2018) (MMRM); Observational period								
PP	159	3.08 (2.68 to 3.48)	—	—	—	—	—	—
AP	78	2.40 (1.89 to 2.92)	0.67 (0.02 to 1.33) 21.9% (0.8% to 40.4%)	.043	—	—	—	—
PA	81	1.88 (1.46 to 2.30)	1.20 (0.62 to 1.78) 39.0% (22.0% to 53.9%)	<.001	0.53 (−0.14 to 1.19) 21.8% (−7.1% to 43.2%)	.124	—	—
AA	158	1.74 (1.42 to 2.06)	1.34 (0.83 to 1.85) 43.5% (29.7% to 55.4%)	<.001	0.67 (0.05 to 1.28) 27.7% (2.8% to 45.5%)	.033	0.14 (−0.39 to 0.67) 7.5% (−25.4% to 30.6%)	.604

Bold type indicates statistically significant values.

vs, versus; *TNSMS*, total nasal symptom medication score; *CI*, confidence interval; *JAU*, Japanese allergy unit; *MMRM*, mixed model for repeated measures; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*, placebo then 5000 JAU; *AA*, 5000 JAU throughout.

1 **Table E5. Symptom relief evaluation during the JC pollen dispersal seasons for the full analysis set (FAS-2019)**

Treatment group	N	Probability (%) * (95% CI)	vs PP		vs AP		vs PA	
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Well days † (Generalized linear ‡)								
First season (2015); Dose-finding period §								
Placebo	257	45.2 (41.9 to 48.6)	—	—	—	—	—	—
5000 JAU	255	53.9 (50.7 to 57.1)	1.42 (1.18 to 1.71)	<.001	—	—	—	—
Second season (2016); Long-term treatment period								
PP	155	38.4 (33.8 to 43.2)	—	—	—	—	—	—
AP	76	50.6 (43.3 to 57.9)	1.65 (1.15 to 2.35)	.006	—	—	—	—
PA	79	55.9 (48.3 to 63.1)	2.03 (1.41 to 2.92)	<.001	1.24 (0.81 to 1.89)	.328	—	—
AA	153	59.8 (55.2 to 64.2)	2.39 (1.81 to 3.14)	<.001	1.45 (1.02 to 2.06)	.037	1.17 (0.82 to 1.68)	.376
Third season (2017); Long-term treatment period								
PP	145	41.5 (36.0 to 47.1)	—	—	—	—	—	—
AP	73	53.1 (45.4 to 60.7)	1.60 (1.09 to 2.35)	.017	—	—	—	—
PA	75	62.9 (54.7 to 70.4)	2.39 (1.59 to 3.61)	<.001	1.50 (0.95 to 2.37)	.085	—	—
AA	146	66.0 (61.1 to 70.6)	2.74 (2.00 to 3.75)	<.001	1.72 (1.18 to 2.50)	.005	1.15 (0.77 to 1.71)	.508
Fourth season (2018); Observational period								
PP	144	40.5 (35.8 to 45.3)	—	—	—	—	—	—
AP	71	44.9 (37.8 to 52.3)	1.20 (0.84 to 1.71)	.317	—	—	—	—
PA	72	55.1 (48.3 to 61.7)	1.81 (1.29 to 2.53)	<.001	1.51 (1.01 to 2.25)	.046	—	—
AA	140	58.2 (53.1 to 63.1)	2.05 (1.54 to 2.73)	<.001	1.71 (1.19 to 2.45)	.004	1.13 (0.81 to 1.60)	.469
Fifth season (2019); Observational period								
PP	139	42.0 (36.6 to 47.6)	—	—	—	—	—	—
AP	69	42.4 (35.0 to 50.2)	1.02 (0.69 to 1.50)	.931	—	—	—	—
PA	70	54.5 (47.2 to 61.6)	1.65 (1.14 to 2.40)	.008	1.63 (1.06 to 2.50)	.026	—	—
AA	138	56.8 (51.3 to 62.2)	1.82 (1.32 to 2.50)	<.001	1.79 (1.22 to 2.63)	.003	1.10 (0.76 to 1.59)	.616
Severe symptom days ¶ (Generalized linear ‡)								
First season (2015); Dose-finding period §								
Placebo	257	18.8 (16.2 to 21.6)	—	—	—	—	—	—

5000 JAU	255	8.1 (6.6 to 10.0)	0.38 (0.29 to 0.51)	<.001	—	—	—	—
<i>Second season (2016); Long-term treatment period</i>								
PP	155	23.8 (19.8 to 28.4)	—	—	—	—	—	—
AP	76	11.0 (7.3 to 16.2)	0.40 (0.24 to 0.66)	<.001	—	—	—	—
PA	79	11.1 (7.4 to 16.5)	0.40 (0.24 to 0.67)	<.001	1.01 (0.53 to 1.91)	.977	—	—
AA	153	6.6 (4.7 to 9.1)	0.22 (0.15 to 0.35)	<.001	0.57 (0.32 to 1.00)	.052	0.56 (0.31 to 1.00)	.050
<i>Third season (2017); Long-term treatment period</i>								
PP	145	21.1 (16.9 to 26.0)	—	—	—	—	—	—
AP	73	9.5 (6.1 to 14.6)	0.39 (0.23 to 0.69)	.001	—	—	—	—
PA	75	7.2 (4.3 to 11.9)	0.29 (0.16 to 0.54)	<.001	0.74 (0.35 to 1.54)	.419	—	—
AA	146	5.9 (3.8 to 9.1)	0.24 (0.14 to 0.41)	<.001	0.60 (0.31 to 1.18)	.137	0.81 (0.39 to 1.68)	.577
<i>Fourth season (2018); Observational period</i>								
PP	144	26.5 (22.2 to 31.3)	—	—	—	—	—	—
AP	71	21.6 (16.3 to 28.1)	0.77 (0.50 to 1.17)	.213	—	—	—	—
PA	72	12.7 (8.9 to 17.9)	0.40 (0.25 to 0.64)	<.001	0.53 (0.31 to 0.90)	.018	—	—
AA	140	12.4 (9.2 to 16.5)	0.39 (0.26 to 0.59)	<.001	0.51 (0.32 to 0.83)	.007	0.97 (0.58 to 1.64)	.910
<i>Fifth season (2019); Observational period</i>								
PP	139	25.5 (20.7 to 31.0)	—	—	—	—	—	—
AP	69	19.0 (13.7 to 25.6)	0.68 (0.43 to 1.10)	.114	—	—	—	—
PA	70	15.1 (10.3 to 21.6)	0.52 (0.31 to 0.87)	.013	0.76 (0.43 to 1.36)	.361	—	—
AA	138	13.6 (10.0 to 18.1)	0.46 (0.30 to 0.71)	<.001	0.67 (0.40 to 1.12)	.127	0.88 (0.50 to 1.53)	.646
<i>Proportion of participants who did not use rescue medication (Logistic regression **)</i>								
<i>First season (2015); Dose-finding period [§]</i>								
Placebo	257	40.5 (34.6 to 46.6)	—	—	—	—	—	—
5000 JAU	255	58.0 (51.9 to 63.9)	2.03 (1.43 to 2.89)	<.001	—	—	—	—
<i>Second season (2016); Long-term treatment period</i>								
PP	155	45.2 (37.5 to 53.1)	—	—	—	—	—	—
AP	76	68.4 (57.2 to 77.8)	2.63 (1.48 to 4.69)	.001	—	—	—	—
PA	79	58.2 (47.1 to 68.6)	1.69 (0.98 to 2.93)	.060	0.64 (0.33 to 1.24)	.189	—	—
AA	153	64.7 (56.8 to 71.9)	2.23 (1.41 to 3.52)	<.001	0.85 (0.47 to 1.52)	.577	1.32 (0.75 to 2.29)	.335
<i>Third season (2017); Long-term treatment period</i>								
PP	145	49.7 (41.6 to 57.7)	—	—	—	—	—	—

AP	73	71.2 (59.9 to 80.4)	2.51 (1.37 to 4.59)	.003	–	–	–	–
PA	75	76.0 (65.1 to 84.3)	3.21 (1.72 to 5.98)	<.001	1.28 (0.61 to 2.66)	.511	–	–
AA	146	77.4 (69.9 to 83.5)	3.47 (2.09 to 5.76)	<.001	1.38 (0.73 to 2.62)	.319	1.08 (0.56 to 2.09)	.815
<i>Fourth season (2018); Observational period</i>								
PP	144	38.9 (31.3 to 47.1)	–	–	–	–	–	–
AP	71	43.7 (32.7 to 55.3)	1.22 (0.68 to 2.17)	.503	–	–	–	–
PA	72	54.2 (42.6 to 65.3)	1.86 (1.05 to 3.29)	.034	1.52 (0.79 to 2.95)	.210	–	–
AA	140	57.9 (49.5 to 65.8)	2.16 (1.34 to 3.47)	.001	1.77 (1.00 to 3.15)	.052	1.16 (0.66 to 2.06)	.608
<i>Fifth season (2019); Observational period</i>								
PP	139	45.3 (37.2 to 53.7)	–	–	–	–	–	–
AP	69	55.1 (43.3 to 66.3)	1.48 (0.83 to 2.64)	.186	–	–	–	–
PA	70	52.9 (41.2 to 64.2)	1.35 (0.76 to 2.41)	.304	0.91 (0.47 to 1.78)	.793	–	–
AA	138	64.5 (56.2 to 72.0)	2.19 (1.35 to 3.55)	.001	1.48 (0.82 to 2.67)	.191	1.62 (0.90 to 2.91)	.106

2 Bold type indicates statistically significant values.

3 vs, versus; *JC*, Japanese cedar; *CI*, confidence interval; *JAU*, Japanese allergy unit; *PP*, placebo throughout; *AP*, 5000 JAU then placebo; *PA*,
4 placebo then 5000 JAU; *AA*, 5000 JAU throughout.

5 * Probability was calculated as [total number of well days or severe symptom days] / ([number of participants]) × [number of days during the
6 *JC* pollen dispersal season]), and was estimated based on a generalized linear model. For participants who did not use rescue medication, the
7 probability was estimated based on a logistic regression model.

8 ** Fixed effect: treatment groups.

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

10 ‡ Generalized linear models using a logit link function, assuming exchangeable (compound symmetry) covariance structure within subjects,
11 with treatment group as a fixed effect.

12 § Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU groups.

13 ¶ Days with at least one symptom evaluated as 4+ for nasal symptoms or 3+ for ocular symptoms.

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15

16

1 **Table E6. Cumulative frequency of rescue medication use during the JC pollen dispersal season for the full analysis set (FAS-2019)**

Treatment group	N	Oral antihistamines				Nasal vasoconstrictors				Ocular antihistamines			
		Mean ± SD	P value			Mean ± SD	P value			Mean ± SD	P value		
			vs PP	vs AP	vs PA		vs PP	vs AP	vs PA		vs PP	vs AP	vs PA
First season (2015); Dose-finding period *													
Placebo	257	10.2 ± 19.1	–	–	–	10.2 ± 27.3	–	–	–	13.0 ± 26.2	–	–	–
5000 JAU	255	2.4 ± 9.8	<.001	–	–	3.0 ± 15.4	<.001	–	–	4.0 ± 11.3	<.001	–	–
Second season (2016); Long-term treatment period													
PP	155	12.6 ± 23.8	–	–	–	12.7 ± 35.6	–	–	–	17.1 ± 33.8	–	–	–
AP	76	2.9 ± 11.4	<.001	–	–	2.3 ± 10.2	.013	–	–	6.5 ± 23.6	<.001	–	–
PA	79	5.1 ± 12.6	.051	.089	–	2.9 ± 9.6	.080	.440	–	4.6 ± 14.7	<.001	.615	–
AA	153	2.3 ± 8.6	<.001	.628	.012	2.0 ± 11.6	.006	.654	.624	3.4 ± 11.6	<.001	.750	.766
Third season (2017); Long-term treatment period													
PP	145	11.6 ± 23.6	–	–	–	13.7 ± 40.7	–	–	–	12.4 ± 29.2	–	–	–
AP	73	2.2 ± 9.1	<.001	–	–	1.5 ± 7.6	.008	–	–	4.9 ± 17.3	0.001	–	–
PA	75	3.2 ± 11.2	<.001	.616	–	2.7 ± 13.6	.006	.853	–	4.3 ± 16.3	0.001	.947	–
AA	146	3.2 ± 14.1	<.001	.257	.629	3.2 ± 19.5	<.001	.330	.475	3.6 ± 18.8	<.001	.762	.770
Fourth season (2018); Observational period													
PP	144	16.5 ± 27.6	–	–	–	19.7 ± 46.2	–	–	–	21.3 ± 39.6	–	–	–
AP	71	8.9 ± 19.9	.038	–	–	10.8 ± 34.6	.518	–	–	16.7 ± 37.0	.374	–	–
PA	72	5.6 ± 13.8	.003	.482	–	6.4 ± 21.9	.127	.405	–	8.0 ± 22.6	.078	.489	–
AA	140	7.4 ± 21.1	<.001	.202	.685	6.9 ± 32.1	.006	.081	.420	10.8 ± 34.9	<.001	.046	.187
Fifth season (2019); Observational period													
PP	139	17.4 ± 30.4	–	–	–	18.3 ± 44.8	–	–	–	19.6 ± 41.5	–	–	–
AP	69	8.7 ± 18.5	.058	–	–	7.4 ± 21.7	.233	–	–	14.5 ± 35.7	.361	–	–
PA	70	6.5 ± 17.0	.091	.825	–	6.5 ± 21.5	.060	.522	–	7.5 ± 19.2	.036	.288	–
AA	138	7.7 ± 22.4	.002	.486	.298	5.0 ± 27.4	.012	.368	.916	9.0 ± 32.8	.001	.064	.516

- 2 *P* values determined by the Wilcoxon rank sum test. Bold type indicates statistically significant values. vs, versus; SD, standard deviation; JAU, Japanese
- 3 allergy unit; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout.
- 4 * Dose-finding period included four groups: placebo, 2000 JAU, 5000 JAU, and 10,000 JAU group.

Table E7. Individual JRQLQ component scores evaluated on March 31 in the fourth and fifth seasons for the full analysis set (FAS-2019)

QOL domain	Mean $\pm$ SD				P value (Linear model vs PP group)		
	PP	AP	PA	AA	AP	PA	AA
<i>Fourth season</i>							
N	137	68	69	130			
Usual daily activities	1.61 $\pm$ 1.19	1.41 $\pm$ 1.09	1.17 $\pm$ 1.19	1.04 $\pm$ 1.14	.231	.010	<.001
Outdoor activities	1.72 $\pm$ 1.36	1.54 $\pm$ 1.34	1.25 $\pm$ 1.29	1.21 $\pm$ 1.36	.362	.020	.002
Social functioning	1.17 $\pm$ 1.13	1.11 $\pm$ 1.14	0.96 $\pm$ 1.07	0.75 $\pm$ 0.98	.707	.183	.001
Impaired sleeping	1.73 $\pm$ 1.49	1.54 $\pm$ 1.41	1.19 $\pm$ 1.35	1.06 $\pm$ 1.22	.346	.008	<.001
Physical problems	1.60 $\pm$ 1.34	1.30 $\pm$ 1.27	1.25 $\pm$ 1.27	1.12 $\pm$ 1.28	.121	.066	.002
Emotional functions	1.50 $\pm$ 1.29	1.29 $\pm$ 1.26	1.11 $\pm$ 1.19	0.96 $\pm$ 1.18	.253	.033	<.001
<i>Fifth season</i>							
N	133	67	67	130			
Usual daily activities	1.44 $\pm$ 1.12	1.31 $\pm$ 1.14	1.05 $\pm$ 1.10	0.94 $\pm$ 1.07	.418	.020	<.001
Outdoor activities	1.53 $\pm$ 1.29	1.41 $\pm$ 1.33	1.11 $\pm$ 1.23	1.01 $\pm$ 1.18	.521	.025	<.001
Social functioning	1.10 $\pm$ 1.10	1.05 $\pm$ 1.16	0.82 $\pm$ 1.00	0.69 $\pm$ 0.93	.770	.073	.002
Impaired sleeping	1.56 $\pm$ 1.34	1.26 $\pm$ 1.29	1.01 $\pm$ 1.21	0.93 $\pm$ 1.19	.108	.004	<.001
Physical problems	1.53 $\pm$ 1.23	1.19 $\pm$ 1.25	1.07 $\pm$ 1.22	0.94 $\pm$ 1.23	.060	.013	<.001
Emotional functions	1.40 $\pm$ 1.22	1.12 $\pm$ 1.10	1.04 $\pm$ 1.13	0.82 $\pm$ 1.04	.097	.034	<.001

JRQLQ, Japanese Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality of life; SD, standard deviation; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout; vs, versus.

Table E8. JRQLQ general state and individual component scores evaluated on March 15 in the fourth and fifth seasons for the full analysis set (FAS-2019)

(A) JRQLQ general state

Evaluation index	n (%)				P value (Wilcoxon rank-sum test vs PP group)		
	PP	AP	PA	AA	AP	PA	AA
<i>Fourth season</i>							
N	139	68	69	131			
0 (Fine)	2 (1.4)	3 (4.4)	4 (5.9)	12 (9.2)	.010	<.001	<.001
1	15 (10.8)	12 (17.6)	21 (30.9)	45 (34.4)			
2	27 (19.4)	18 (26.5)	18 (26.5)	35 (26.7)			
3	57 (41.0)	24 (35.3)	19 (27.9)	30 (22.9)			
4 (Crying)	38 (27.3)	11 (16.2)	6 (8.8)	9 (6.9)			
Missing data	0	0	1	0			
<i>Fifth season</i>							
N	136	67	68	131			
0 (Fine)	2 (1.5)	2 (3.0)	3 (4.4)	7 (5.3)	.033	.001	<.001
1	21 (15.6)	14 (20.9)	16 (23.5)	36 (27.5)			
2	26 (19.3)	16 (23.9)	21 (30.9)	47 (35.9)			
3	52 (38.5)	27 (40.3)	21 (30.9)	31 (23.7)			
4 (Crying)	34 (25.2)	8 (11.9)	7 (10.3)	10 (7.6)			
Missing data	1	0	0	0			

(B) Individual component scores

QOL domain	Mean $\pm$ SD				P value (Linear model vs PP group)		
	PP	AP	PA	AA	AP	PA	AA
<i>Fourth season</i>							
N	139	68	68	131			
Usual daily activities	1.67 $\pm$ 1.19	1.17 $\pm$ 0.97	0.90 $\pm$ 1.08	0.79 $\pm$ 0.99	.002	<.001	<.001
Outdoor activities	1.72 $\pm$ 1.33	1.38 $\pm$ 1.26	1.10 $\pm$ 1.20	0.95 $\pm$ 1.16	.065	<.001	<.001
Social functioning	1.06 $\pm$ 1.05	0.81 $\pm$ 1.00	0.76 $\pm$ 1.05	0.57 $\pm$ 0.88	.091	.039	<.001
Impaired sleeping	1.60 $\pm$ 1.41	1.15 $\pm$ 1.26	1.13 $\pm$ 1.28	0.73 $\pm$ 1.05	.015	.011	<.001
Physical problems	1.71 $\pm$ 1.41	1.14 $\pm$ 1.11	1.07 $\pm$ 1.18	0.86 $\pm$ 1.11	.002	<.001	<.001
Emotional functions	1.52 $\pm$ 1.28	1.10 $\pm$ 1.10	1.00 $\pm$ 1.14	0.77 $\pm$ 1.12	.018	.003	<.001
<i>Fifth season</i>							
N	135	67	68	131			
Usual daily activities	1.60 $\pm$ 1.21	1.43 $\pm$ 1.18	1.02 $\pm$ 1.11	0.89 $\pm$ 1.01	.299	<.001	<.001
Outdoor activities	1.60 $\pm$ 1.30	1.48 $\pm$ 1.32	1.13 $\pm$ 1.17	0.99 $\pm$ 1.10	.530	.010	<.001
Social functioning	1.06 $\pm$ 1.08	0.99 $\pm$ 1.13	0.77 $\pm$ 0.91	0.64 $\pm$ 0.90	.645	.058	<.001
Impaired sleeping	1.64 $\pm$ 1.41	1.24 $\pm$ 1.31	0.97 $\pm$ 1.20	0.93 $\pm$ 1.09	.034	<.001	<.001
Physical problems	1.53 $\pm$ 1.35	1.30 $\pm$ 1.25	1.13 $\pm$ 1.17	0.85 $\pm$ 1.13	.215	.029	<.001
Emotional functions	1.45 $\pm$ 1.24	1.14 $\pm$ 1.10	1.01 $\pm$ 1.13	0.76 $\pm$ 1.01	.063	.009	<.001

JRQLQ, Japanese Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality of life; SD, standard deviation; PP, placebo throughout; AP, 5000 JAU then placebo; PA, placebo then 5000 JAU; AA, 5000 JAU throughout; vs, versus.

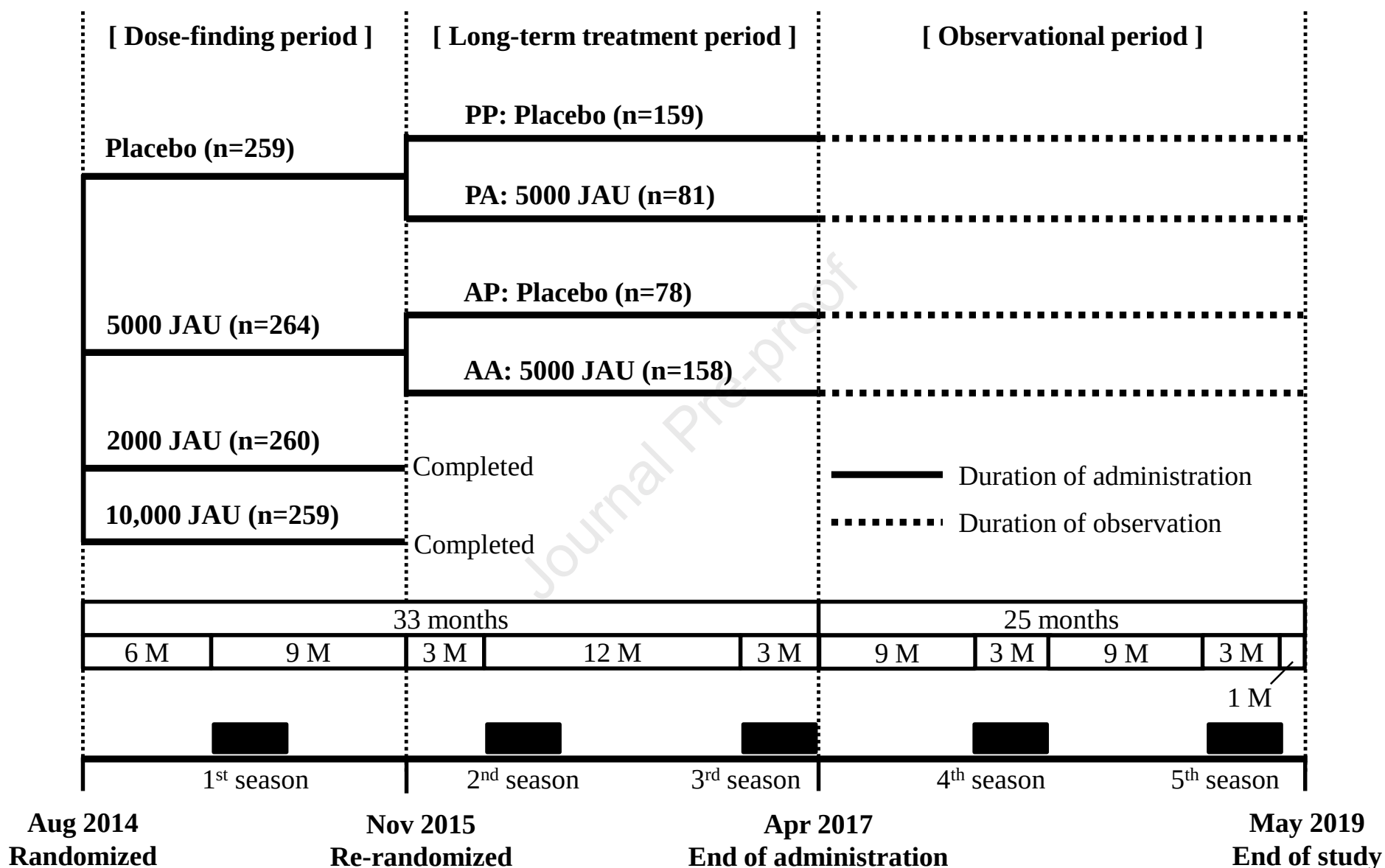


Fig. E2

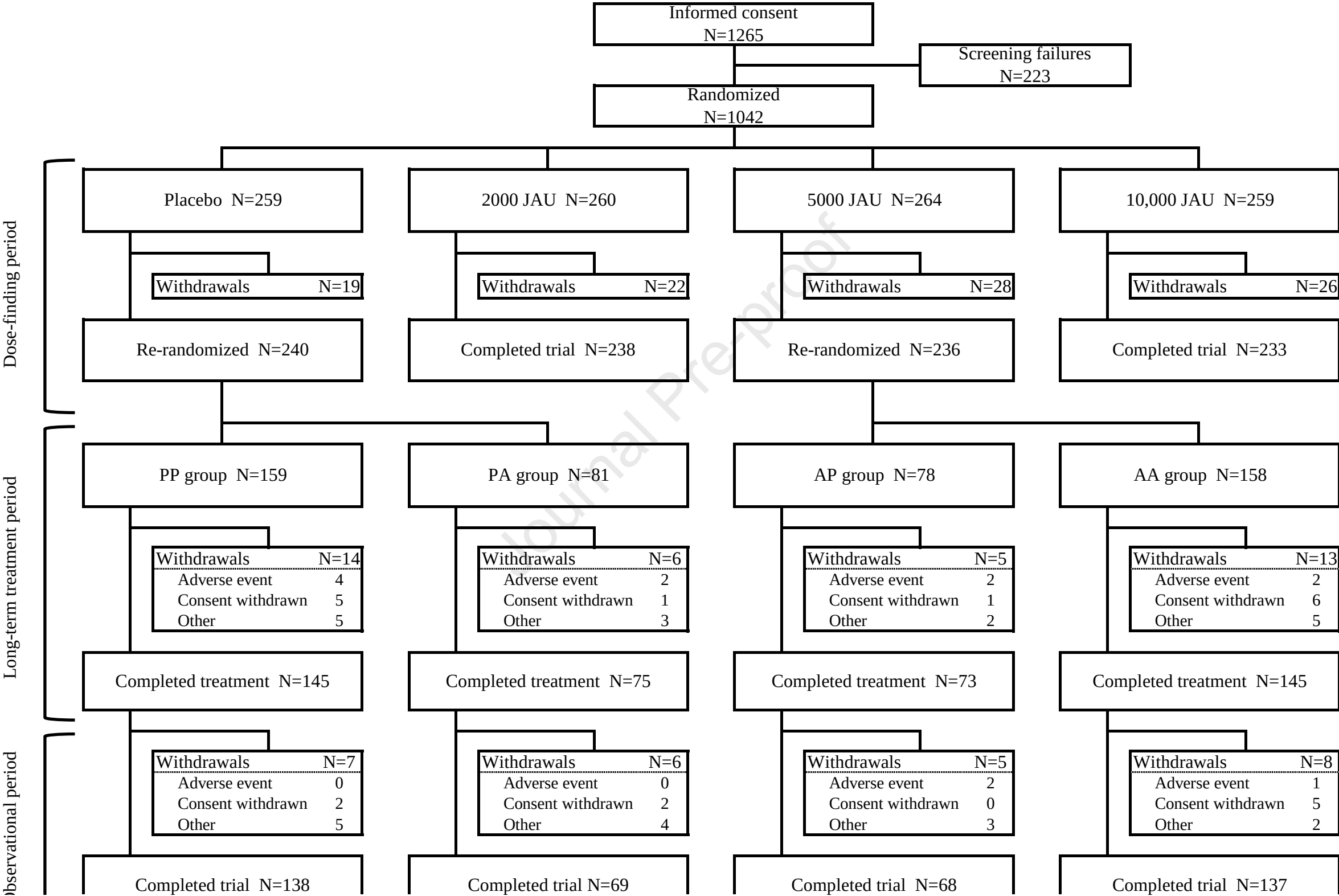
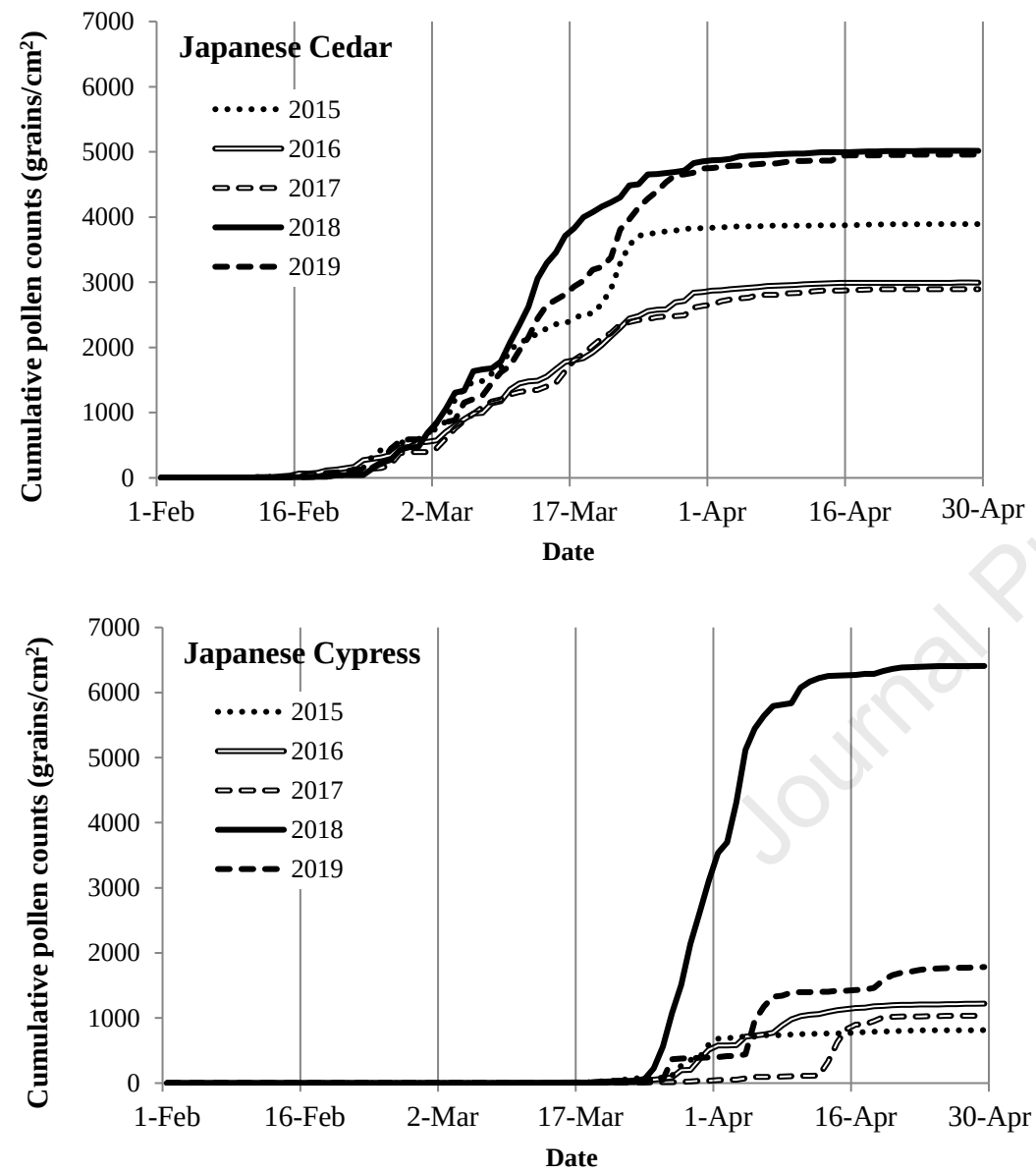


Fig. 12



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Fig. E3



Supplementary text online repository

Title: Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets

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25

26 **Abbreviations**

27 AA group - Active-to-active (5000 JAU re-randomized to 5000 JAU)

28 AP group - Active-to-placebo (5000 JAU re-randomized to placebo)

29 JAU - Japanese allergy unit

30 JC - Japanese cedar

31 JRQLQ - Japanese Rhinoconjunctivitis Quality of Life Questionnaire

32 PA group - Placebo-to-active (placebo re-randomized to 5000 JAU)

33 PP group - Placebo-to-placebo (placebo re-randomized to placebo)

34 SLIT - Sublingual immunotherapy

35 TNSMS - Total nasal symptom and medication score

36 TOSMS - Total ocular symptom and medication score

37

Methods

Trial design

This randomized, double-blind, placebo-controlled trial (JapicCTI-142579) complied with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the clinical review committee of each medical institution. Written consent was obtained from all subjects or, in the case of minor subjects, their legal representatives. The sponsor (Torii Pharmaceutical Co., Japan), subjects, legal representatives, investigators, and those involved in executing the study were blinded until the database was locked at the end of the fifth JC pollen dispersal season.

Details of the trial have been reported previously.^{E1,E2} In brief, the trial included dose-finding, long-term treatment, and observational phases and encompassed the JC pollen dispersal seasons over 5 years (2015–2019) (Fig. E1). Between August 2014 and November 2015, which encompassed the first JC pollen dispersal season, four cohorts of patients were administered SLIT containing 2000, 5000, or 10,000 Japanese Allergy Units (JAU) or placebo to determine the optimal drug dose. In November 2015, approximately 3 months before the start of the second JC pollen dispersal season, patients in the optimal dose group (5000 JAU, A group) and the placebo group (P group) were re-randomized at a ratio of 2:1:1:2 to AA:AP:PA:PP groups and were administered P or A until the end of the third JC pollen dispersal season (end of April 2017). The duration of treatment with active drug was 33 months (August 2014 to April 2017) for the AA group, which encompassed the first through third JC pollen seasons; 15 months (August 2014 to November 2015) for the AP group, which encompassed only the first season; and 18 months (November 2015 to April 2017) for the PA group, which encompassed the second and third seasons. Safety and efficacy observations were continued during the fourth and fifth seasons and the trial concluded in May 2019.

Study drug

The study drug was a fast-dissolving lyophilized SLIT tablet manufactured by ALK-Abelló (Hørsholm, Denmark). Subjects were administered one tablet daily, which was held sublingually for 1 min before swallowing. Patients received the first administration at the institution and were evaluated by the physician for 30 min after dosing. As previously reported,^{E1} the dose-finding period included an initial period of drug titration. Participants assigned to the 5000 JAU group took a 5000 JAU JC pollen SLIT tablet every day, after taking a 2000 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 2000 JAU and 5000 JAU tablets for 1 week each.

Oral antihistamines, eye drops, and nasal vasoconstrictors were provided to the subjects as rescue medications and were to be used only when intolerable symptoms developed. Children who could not take tablets were provided with oral antihistamines in dry syrup (powder) form.

Trial population

Subject enrollment was restricted to residents of Tokyo and its suburbs to minimize variations in natural exposure to JC pollen. Inclusion criteria have been previously reported^{E1,E2} and included age 5–64 years, serum JC pollen-specific IgE level of ≥ 3.5 UA/mL, and symptoms of JC pollinosis during the previous two JC pollen dispersal seasons. Key exclusion criteria were comorbidity with perennial allergic rhinitis, drug-induced rhinitis, vasomotor rhinitis, or nonallergic rhinitis requiring any treatment; past treatment with JC pollinosis-specific immunotherapy; laser therapy or surgery to treat nasal symptoms in the last 3 years; bronchial asthma attack in the last 5 years; or IgE levels of ≥ 50 UA/mL specific for *Dermatophagoides*

farinae, *Dermatophagoides pteronyssinus*, cat dander, dog dander, Japanese cypress, orchard grass, or Japanese alder.

Outcomes

JC pollen counts were performed in central Tokyo using the Durham method. Nasal and eye symptom evaluation was based on the Japanese guidelines for allergic rhinitis 2017^{E3} and on previous experience with the clinical development of JC pollen SLIT drops.^{E4} Scores for sneezing, runny nose, and congested nose ranged from 0 to 4, and scores for itchy eyes and watery eyes ranged from 0 to 3. Rescue medication was scored 0 for no use and 3 for use. Subjects entered details of their symptoms and rescue medication use in an electronic patient diary every day from January 8 to April 30 of each year. The maximum score for the primary endpoint of Total Nasal Symptom and Medication Score (TNSMS) was 18, based on a maximum score of 12 for symptoms and 6 for rescue medication use (antihistamine tablets and nasal vasoconstrictors). The maximum score for Total Ocular Symptom and Medication Score (TOSMS) was 9, based on a maximum score of 6 for symptoms and 3 for rescue medication use (eye drops). Details of the scoring scale are available in our previous reports.^{E1,E2} Well days were defined as days when all symptoms were scored 0 or 1 and no rescue medications were used, and severe symptom days were defined as days when at least one symptom was given a maximum score. Subjects also completed the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ)^{E3,E5} twice in each year (March 15 and March 31).

Statistical analysis

The basis for the sample size was described previously.^{E1} In brief, the sample size for the dose-

finding study was based on the results of the JC pollen SLIT drops trial^{E4} and was set at a minimum of 230 patients/group to allow for withdrawal during the treatment period. No formal sample size calculation was performed for the long-term treatment period, which comprised all participants who completed the dose-finding study. The statistical analysis plans for the dose-finding and long-term treatment periods were set before initiation of study drug administration and after treatment cessation, respectively.

We reported that a linear model with the treatment groups as explanatory variables was applied to the endpoint in the first season, which was to determine the optimal dose. Details of the statistical analyses in the first season are presented in our previous publication.^{E1} Thereafter, the primary endpoint was TNSMS during the peak symptom period in the fifth season (2019). In the primary analysis, we applied mixed-model repeated measures (MMRM) with all TNSMS data from all seasons (2015–2019) as the response variables. The treatment group, season, and treatment-by-seasons interactions were included as fixed effects. The variance structure was an unstructured correlation, and the computation method for covariance matrices of fixed effects was a robust (sandwich) covariance matrix estimator. Paired comparisons were performed between four groups based on the least squares mean; a closed testing procedure was performed to adjust for multiplicity in the primary analysis following a sequential order: AA vs PP, PA vs PP, AP vs PP, AA vs AP, and AA vs PA. The primary evaluation set was the full analysis set (FAS) and included participants whose TNSMS during the peak symptom period in 2015 had been measured at least once (FAS-2019). The same analyses were applied to the analysis of symptoms, medications, and combined scores in the peak symptom period and JC pollen dispersal season for all seasons (2016 to 2019), after re-randomization in the same population (FAS-2019). Fieller's theorem was used for calculating the confidence interval for the rate of decrease in the least squares mean.^{E6}

To determine rescue medication use, we employed a logistic regression model with

the treatment group as a fixed effect. Well days and severe symptom days were analyzed by generalized linear models using a logit link function, assuming exchangeable (compound symmetry) covariance structure within subjects, with the treatment group as a fixed effect. Cumulative number of rescue medications used, global evaluation by physicians and subjects, and JRQLQ general state scores were analyzed using Wilcoxon's rank-sum test. JRQLQ component scores were analyzed using linear models with the component score as the dependent variable and treatment group as a fixed effect.

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

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Figure Legends

Figure E1.

Trial design. Black boxes represent the first through fifth JC pollen dispersal seasons. Participants recorded symptom and medication use scores in an electronic diary every day between January 8th and April 30th of each year. The duration of treatment with active drug was: 33 months (August 2014 to April 2017) for the AA group, which encompassed the first through third JC pollen seasons; 15 months (August 2014 to November 2015) for the AP group, which encompassed only the first season; and 18 months (November 2015 to April 2017) for the PA group, which encompassed the second and third seasons.

Figure E2.

Participant disposition.

Reasons for screening failure and withdrawal during the dose-finding period have been published previously.^{E1} “Other” reasons for withdrawal during the long-term treatment and observational periods included “lack of efficacy,” “pregnancy,” “moved from the trial area,” and “lost to follow-up”.

Figure E3.

Cumulative pollen counts for each year of the trial (2015–2019).

Japanese cedar (JC) and Japanese cypress (JCY) pollen counts in central Tokyo were measured using a Durham sampler. For JC pollen, the cumulative counts were average during the first through third seasons (2894 to 3892 grains/cm²) and above average during the fourth and fifth seasons (5016 and 4960 grains/cm², respectively). JCY pollen counts showed a similar pattern to those for JC pollen in the first, second, third, and fifth seasons (815, 1221, 1041, and 1784 grains/cm², respectively), but were extremely high in the fourth season (2018; 6408 grains/cm²).