

Accepted Manuscript

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PII: S0091-6749(16)31294-5

DOI: [10.1016/j.jaci.2016.09.043](https://doi.org/10.1016/j.jaci.2016.09.043)

Reference: YMAI 12449

To appear in: *Journal of Allergy and Clinical Immunology*

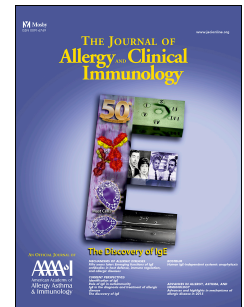
Received Date: 29 March 2016

Revised Date: 2 September 2016

Accepted Date: 21 September 2016

Please cite this article as: Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, Konno A, Efficacy and Safety of the SQ House Dust Mite SLIT-tablet in Japanese Adults and Adolescents with House Dust Mite-induced Allergic Rhinitis, *Journal of Allergy and Clinical Immunology* (2016), doi: [10.1016/j.jaci.2016.09.043](https://doi.org/10.1016/j.jaci.2016.09.043).

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Efficacy and Safety of the SQ House Dust Mite SLIT-tablet in Japanese Adults and Adolescents with House Dust Mite-induced Allergic Rhinitis

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21 **Funding:** This trial was funded by Torii, Tokyo, Japan.

22

23 **Role of sponsor:** The trial was sponsored by Torii, Tokyo, Japan, who assumes overall
24 responsibility for the trial and has been involved in both trial design and conduct.

25

26 **ABSTRACT** <max 250 words, current 250 (excluding headlines)>

27 **Background:** The SQ HDM SLIT-tablet has been approved in 11 European countries and Japan for
28 patients suffering from house dust mite (HDM) respiratory allergic disease.

29 **Objective:** This trial was conducted to confirm efficacy and safety in Japanese patients with
30 moderate to severe HDM allergic rhinitis (AR).

31 **Methods:** The trial was a randomized, double-blind, placebo-controlled trial including 946 Japanese
32 adults and adolescents (12-64 years). Subjects were randomly assigned to daily treatment with SQ
33 HDM SLIT-tablet at a dose of 10,000 JAU or 20,000 JAU or with placebo (1:1:1). Primary endpoint
34 was the total combined rhinitis score (TCRS) composed of AR symptom and medication scores, during
35 the efficacy evaluation period. Symptom and medication scores of AR and conjunctivitis, rhinitis quality
36 of life, and symptom-free and -severe days were evaluated as secondary endpoints.

37 **Results:** Analysis of the primary endpoint demonstrated statistically significant reductions of the TCRS
38 of 1.15, 22% ($p<.001$) in the 10,000 JAU and 0.99, 19% ($p<.001$) in the 20,000 JAU compared to
39 placebo. The statistically significant treatment effect was evident from 12 weeks of treatment and
40 onwards. All secondary endpoints, except AR medication score, were statistically significant in favor of
41 active treatment compared to placebo. *Post hoc* analysis of TCRS in adolescents showed the same
42 efficacy as adults ($p<.05$). The treatment was well-tolerated both adults and adolescents.

43 **Conclusion:** The trial confirmed efficacy and safety profile of the SQ HDM SLIT-tablet in Japanese

adult and adolescent patients with moderate to severe HDM AR. These data support the robust efficacy and safety profile of previously reported European data.

Clinical implications <max 30 words, current 30 words>

The results confirmed the SQ HDM SLIT-tablet is tolerable for at-home use and reduces symptoms in adults and adolescents with moderate to severe HDM AR to a clinically relevant degree.

Capsule Summary <1–2 sentences max 35 words, current 34 words>

This trial confirmed efficacy and safety of the SQ HDM SLIT-tablet in Japanese adults and adolescents with moderate to severe HDM AR. TCRS was reduced from week 12 and throughout the 1 year trial.

Key Words <max 10 words, current 10 key words>

Allergy immunotherapy, AIT, sublingual immunotherapy tablet, SLIT, house dust mite, HDM, allergy, allergic rhinitis, conjunctivitis, adolescent

Abbreviations

ADR Adverse drug reaction

AE Adverse event

62	AR	Allergic rhinitis
63	AIT	Allergy immunotherapy
64	CHMP	Committee for Medicinal Products for Human Use
65	<i>D. farinae</i>	<i>Dermatophagoides farinae</i>
66	<i>D. pteronyssinus</i>	<i>Dermatophagoides pteronyssinus</i>
67	EMA	European medicines agency
68	FAS	Full analysis set, observed data
69	FDA	The food and drug administration
70	HDM	House dust mite
71	ITT	Intention-to-treat
72	JAU	Japanese allergy unit
73	JCP	Japanese cedar pollinosis
74	JRQLQ	Japanese rhinoconjunctivitis quality of life questionnaire
75	LME	Linear mixed effect
76	LSD	Least significant difference
77	MCID	Minimum clinical important difference
78	MMRM	Mixed model repeated measures
79	PPS	Per-protocol analysis set

80	SAE	Serious adverse event
81	SCIT	Subcutaneous immunotherapy
82	SLIT	Sublingual immunotherapy
83	TCRS	Total combined rhinitis score
84	WAO	The World Allergy Organization

85

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Introduction

Allergy immunotherapy (AIT) modulates basic immunologic mechanisms of the allergic disease and is recognized as the only treatment option with the potential to provide long-term, post-treatment benefits and alter the natural course of allergic disease.¹ House dust mites (HDMs) are major perennial allergen sources and have been found worldwide.²⁻⁵ Although there are large inter-regional differences regarding the relative abundance of the 2 major HDM species, *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*), the majority of HDM-allergic patients are cosensitized to both species.⁶ Furthermore, no differences in the sensitization pattern have been reported for HDM allergen components over the world,⁷ and therefore AIT can offer the same treatment option worldwide for HDM-induced respiratory allergy.

In Japan, the prevalence of perennial allergic rhinitis (AR) is 23% mainly composed of young population.⁸ However, AIT has not been widely practiced so far due to the disadvantages of subcutaneous immunotherapy (SCIT) such as need for frequent hospital visits before reaching the maintenance phase, pain caused by injections and the risk of systemic reactions. Therefore, most of the patients have been treated by pharmacological therapy when they have intolerable symptoms. In 2014, a new treatment option with the introduction of a sublingual immunotherapy (SLIT) product

for Japanese cedar pollinosis (JCP)⁹ was presented. The goal of AIT is to relieve symptoms by modulating the immunological mechanisms of the allergic disease, and ultimately to provide long-term disease modification.¹⁰⁻¹² This may also contribute to prevention of new sensitizations.^{13,14}

Successful AIT therapy for HDM AR is thus expected to improve the treatment environment for allergic diseases.

The efficacy and safety of the SQ HDM SLIT-tablet was proven in European patients suffering from HDM AR¹⁵ and the present trial was conducted to evaluate the efficacy and safety with up-dosing regimen in a Japanese population. In Europe and the U.S., the approved SQ HDM SLIT-tablet treatment regimens do not include up-dosing, and with the Japanese trial reported here the SQ HDM SLIT-tablet is the first allergy immunotherapy tablet to be evaluated for clinical efficacy and safety in large comparable double-blind, placebo-controlled trials with and without up-dosing (TO-203, Torii, Japan; ALK, Denmark; Merck & Co., Inc. USA).

118 **Methods**

119 *Clinical trial design*

120 This was a randomized, parallel-group, double-blind, placebo-controlled trial in Japan, identified by
121 JapicCTI number 121848. Ninety sites participated in this trial and 946 subjects were randomly
122 assigned to daily treatment with SQ HDM SLIT-tablet at a dose of 10,000 JAU or 20,000 JAU or with
123 placebo (1:1:1). Because there were limited AIT experience among Japanese physicians and
124 patients, a 2-step dose-escalation was chosen though the safety profile was similar in the
125 fixed-dose groups and the dose-escalation group in Japanese phase I trial. Based on the safety
126 profiles of the European phase I trials,¹⁶ 3,300 JAU (2 SQ-HDM) was selected as the initial dose for
127 a week, followed by upward titration of the dose to 10,000 JAU (6 SQ-HDM), and for subjects
128 randomized to the 20,000 JAU (12 SQ-HDM) group, a further upward titration was performed again
129 1 week after treatment with 10,000 JAU. During the up-dosing, patients were provided with weekly
130 packages of the investigational medicinal product or placebo to keep the blinding. Subjects
131 therefore received their randomized treatment for approximately 12 months. To obtain information
132 regarding symptom and medication scores in a timely manner, an electronic diary system was used.
133 The trial design is shown in Fig 1.

134 The trial was designed and conducted in accordance with the Declaration of Helsinki¹⁷ and Good
135 Clinical Practice guidelines.

136

137 *Subjects*

138 Patients were recruited between June and October 2012. They were registered to the run-in period
139 from September 1st through to November 15th. The trial population comprised adults and
140 adolescents (12-64 years) suffering from moderate to severe HDM AR, diagnosed by a positive
141 nasal provocation test and a positive specific IgE against *D. pteronyssinus* and/or *D. farinae* (HDM
142 specific IgE ≥ 3.5 kU/L) with at least 1 year medication history for AR. The positive assessment of
143 nasal provocation test was defined as there were at least two positive symptoms of three symptoms,
144 sneezing/itchy nose, swelling pallor of inferior concha mucosa, watery discharge, within 5 minutes
145 after placing an allergen paper disc on the inferior concha mucosa without positive reactions of a
146 control paper disc previously conducted. Moderate to severe HDM AR symptoms were defined as
147 an AR symptom score of at least 7 over at least 7 of the 14-day run-in period without any
148 symptomatic treatment.

149 Subjects were excluded from the study if they had cosensitizations detected by $50 \text{ kU/L} \leq$ of specific
150 IgE in any of the following allergens, cedar, cypress, alder, cocksfoot, ragweed, mugwort, Japanese
151 hop, cockroach, Candida, Aspergillus, Alternaria, dog hair, or cat hair. Subjects who had clinically
152 relevant history of symptomatic AR due to the allergens mentioned above were also excluded even
153 if their specific IgEs were the range of $0.7 \leq$ to $< 50 \text{ kU/L}$ except spring seasonal allergens, cedar,

cypress and alder. The trial did not allow enrolment of patients with a medical history of asthma, including use of asthma medication and/or asthma exacerbation within 2 years. Details on the main selection criteria are available in the Methods section in the online repository.

Standardization in Japan

The Japanese Society of Allergology task force standardized the HDM AIT vaccine in 2014.¹⁸ To standardize SQ HDM SLIT-tablet, allergen contents of the standardized HDM AIT vaccine was firstly measured by manufacture's methods to calculate the correction value. As a result of the adjustment by the correction value and the titer of the standardized HDM AIT vaccine, a nominal strength of 3,300 Japanese Allergy Unit (JAU) has the same potency as 2 SQ-HDM, 10,000 JAU as 6 SQ-HDM, and 20,000 JAU as 12 SQ-HDM.

Intervention Medication

The intervention medication, SQ HDM SLIT-tablet (TO-203, Torii, Japan/ ALK, Denmark/ Merck & Co., Inc. USA), was manufactured and provided by ALK, Denmark. The SQ HDM SLIT-tablet is a fast-dissolving freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *D. pteronyssinus* and *D. farinae*. Thus, the tablet contains the broadest possible spectrum of *D. pteronyssinus* and *D. farinae* major and minor allergens. A highly standardized production process

ensures a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2.¹⁹ The unit term used in clinical trials before obtaining approval in each region was “DU” (development unit). Following regulatory approval, the unit in Japan is “JAU” in accordance with the standardization by Japanese Society of Allergology and in Europe the unit is “SQ-HDM”.

The first administration of each dose was given at each clinical site to allow supervision lasting at least 30 minutes in the interest of safety. Subjects were instructed to take 1 tablet daily sublingually, and to keep the dissolved saliva in their mouth for 1 minute. The placebo tablets were similar to the active intervention medication with regard to appearance, smell, and taste.

To treat intolerable symptoms of AR or conjunctivitis, rescue medications (i.e. allergy pharmacotherapy; antihistamine tablets and eye drops, nasal steroid) were provided by the trial sponsor to randomized subjects. Allergy pharmacotherapy was allowed only when a subject felt that “symptoms were intolerable”, and prohibited preventive use.

Outcomes

A total of six allergic symptoms, four rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two conjunctivitis symptoms (gritty feeling/red/itchy eyes, watery eyes) were measured on a scale from 0–3, from no symptoms to severe symptoms based on the EMA guideline.²⁰ For the medication score, subjects reported their use of specific pharmacotherapy. The primary endpoint was

the total combined rhinitis score (TCRS), i.e. sum of rhinitis symptoms and medication score (range: 0–24). Details on the scoring scales are available in the Methods section with Table E1, E2 and E3 in the online repository.

Subjects entered those data every evening during the run-in period, during the 2 weeks following the visits at weeks 4, 12, 20, 28, and 36, and during the primary efficacy evaluation period (the last 8 weeks of the 52-week treatment period) **Fig 1**. The primary efficacy evaluation period was from July to November.

Japanese rhinoconjunctivitis quality of life questionnaire (JRQLQ)⁸ was assessed at randomization, weeks 4, 28, 44, and 52 at clinical sites.

HDM specific IgE and IgG4 were measured to confirm the specific immunological response (to be published separately).

The safety profile was assessed by gathering information regarding treatment emergent adverse events.

Statistics

The sample size calculation was based on the results of a previous SQ HDM SLIT-tablet trial.²¹

There was a power of approximately 92% to detect a difference between 10,000- and 20,000-JAU combined and placebo with 300 subjects in each group including an estimated 10% discontinuation

rate (details in the online repository). The primary analysis was a linear mixed effect (LME) model using the AR symptom score at baseline and the treatment group as fixed effects and clinical site as a random effect. The primary analysis set was the full analysis set (FAS), which included subjects who entered at least 80% of information regarding symptom score and medication use into the electronic diary during the last 8 weeks of the treatment period. Additional analysis sets for the primary endpoint were the per-protocol analysis set (PPS) with subjects who had no significant protocol deviation, analyzed using a LME model, and subjects who recorded symptom score and medication use at least once during the course of the trial were handled as intention-to-treat (ITT), analyzed using mixed model repeated measures (MMRM). AR symptom score, the pre-specified key secondary endpoint, was analyzed in a similar manner to the analysis of the primary endpoint. Multiplicity for the primary analysis was controlled for using Fisher's least significant difference (LSD) procedure.²² Details on the statistical analyses are available in the Methods section with Table E4 in the online repository.

Results

Population

Subject disposition is shown in **Fig 2**. Informed consent was obtained from 1740 patients, of whom 946 subjects were randomized as follows: 313 in the 10,000 JAU group, 314 in the 20,000 JAU group, and 319 in the placebo group. The total number of withdrawals was highest in the placebo group, and so was the number of withdrawals due to adverse events (AEs).

Subject baseline characteristics are shown in **Table 1**. This trial was designed to include patients aged 12-64 years; those aged 12-17 years accounted for $\geq 30\%$ of the subjects in each group. In all 3 groups, the mean age of subjects was approximately 27 years, and the mean duration of HDM AR was around 10 years. Concerning HDM-specific IgE antibody levels in each treatment group, one third of the subjects were assessed as < 17.5 kU/L, one third as the range of $17.5 \leq$ to < 50 kU/L, and the remaining one third as ≥ 50 kU/L in terms of *D. farinae* and *D. pteronyssinus*. The percentage of subjects with monosensitization to HDM was 24.3% in the 10,000 JAU group and 18.2% in the 20,000 JAU group. In polysensitized subjects, the most common other allergen based on specific IgE antibody levels was Japanese cedar pollen (67%), followed by Japanese cypress pollen (34%), cats (26%), orchard grass (23%), and dogs (15%). The electronic diary compliance was $\geq 80\%$ in all subjects except for 1 subject in the 10,000 JAU group during the last 8 weeks of the treatment period.

241

242 *Efficacy*

243 The primary endpoint was TCRS during the last 8 weeks of the treatment period (primary evaluation
244 period). The results of the analysis are shown in **Table 2**.

245 In the FAS, the primary analysis set, the absolute differences from the placebo group in adjusted
246 means were 1.15 ($P<.001$) in the 10,000 JAU group and 0.99 ($P<.001$) in the 20,000 JAU group.

247 The relative differences to the placebo group were 22% and 19% in the 10,000 and 20,000 JAU
248 groups, with 95% confidence interval (CI) upper limits of 13% and 10%, respectively. These results
249 were supported by LME and MMRM analyses in the PPS and ITT.

250 The difference in adjusted mean AR symptom scores during the treatment period between placebo
251 and active groups tended to increase with increasing treatment duration. The adjusted mean AR
252 symptom scores at week 12 in both active groups were significantly different from those in the
253 placebo group, and this significant difference was maintained until the end of treatment. The
254 symptom scores for AR and conjunctivitis during the primary evaluation period in both active groups
255 were statistically significantly lower than those in the placebo group in terms of all symptoms (**Fig**
256 **3**).

257 The TCRSs during the primary evaluation period were compared between adults aged 18-64 years
258 and adolescents aged 12-17 years (**Fig 4**). The differences from the placebo group in adjusted

mean in adults and adolescents were 1.21 and 1.11 in the 10,000 JAU group and 1.04 and 0.96 in the 20,000 JAU group ($P<.05$; *post hoc* analysis), showing a similarity between both age populations.

The results of the secondary endpoints are shown in **Table 3**. The analysis results of the key secondary endpoint supported those of the primary endpoint. Of other pre-specified secondary endpoints, AR medication score showed no significant difference between the placebo group and active groups. Meanwhile, both symptom and medication scores for conjunctivitis showed significant differences between the placebo group and both active groups and, as a result, so did the combined conjunctivitis score. The score for general state in the JRQLQ at the end of treatment (visit at week 52) also showed a significant difference between the placebo group and both active groups.

Safety

The results of safety analyses are summarized in **Table 4**. Serious adverse events (SAEs) occurred in 3 groups at similar incidences, while no serious adverse drug reactions (ADRs) assessed by investigators as possibly related to SQ HDM SLIT-tablet occurred. There were no severe ADRs or severe AEs except for 1 case (tooth hypoplasia) in the 10,000 JAU group. No marked differences were noted in the incidence of ADRs between the 10,000 (63.6%) and 20,000 (63.7%) JAU groups.

277 Most of the ADRs reported in either group were mild in severity, and the most commonly observed
278 ADRs were mouth edema, oral pruritus, and throat irritation. In this trial, the following 4 events were
279 predefined as significant AEs: anaphylactic reaction, asthma, AEs leading to discontinuation, and
280 ADRs leading to interruption. An anaphylactic reaction was reported in 1 subject in the placebo
281 group. On the day of the onset of the event, this subject failed to take the study drug and consumed
282 food to which the subject had a history of allergic reaction. Therefore, a causal relationship to the
283 study drug was ruled out for the event. This trial excluded patients with concurrent asthma or a
284 history of treatment for or attacks of asthma within the previous 2 years. Nevertheless, 8 subjects
285 were diagnosed with asthma during the treatment period: 3 in the 10,000 JAU group, 2 in the
286 20,000 JAU group, and 3 in the placebo group; showing no marked difference in incidence among
287 the 3 groups. The incidence of AEs leading to discontinuation was highest in the placebo group and
288 lowest in the 20,000 JAU group. The incidence of ADRs leading to interruption was higher in both
289 active groups than in the placebo group, and many of these ADRs were oral events observed at an
290 early stage of treatment. After an interruption of several days, most of the affected subjects
291 resumed treatment and continued treatment until the end of the trial.

292 The ADRs reported were analyzed by incidence and by severity for adults aged 18-64 years and for
293 adolescents aged 12-17 years (**Fig 4**). No marked differences were noted in the incidence or
294 severity of ADRs between both age populations, indicating the highly safe profile of the study drug

295 in the subjects aged 12-64 years.

Discussion

This randomized, double-blind, placebo-controlled phase II/III trial is the first trial with the SQ HDM SLIT-tablet in a Japanese population. The trial revealed a statistically significant reduction in TCRS for both active doses of the SQ HDM SLIT-tablet compared to placebo in a population of Japanese adults and adolescents with moderate to severe HDM AR. The reduction in TCRS compared to placebo (1.15 for the selected dose 10,000 JAU) was similar in magnitude to what was recently observed with the SQ HDM SLIT-tablet in an adult European population with moderate to severe HDM AR (1.18 for 6 SQ-HDM/10,000 JAU).¹⁵ In the trial by Demoly et al, the reduction in TCRS induced by the SQ HDM SLIT-tablet was equally driven by reductions in AR medication score and symptom score, whereas in the current trial, the TCRS reduction was almost exclusively driven by a reduction in AR symptoms. This difference may reflect the slightly different populations in the two trials. The subjects in the European trial had moderate to severe AR despite frequent use of allergy pharmacotherapy, which is in contrast to the current trial where the Japanese subjects had a very low habitual use of allergy pharmacotherapy. The results of the current trial is, despite differences in scoring scales, comparable to what was shown in a trial with a different HDM SLIT-tablet in a similar population with low use of allergy pharmacotherapy.²³

To date there is no general consensus regarding the optimal methodology to set the minimum

314 clinical important difference (MCID) specific for TCRS in AIT trials in perennial allergic rhinitis. The
315 Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency
316 (EMA) has therefore decided not to provide fixed values for the definition of a clinically relevant
317 difference in the primary endpoint between active and control population, but rather ask the
318 investigator to predefine and justify their specific approach handling endpoints. In the trial by
319 Demoly et al, a MCID was pre-defined as the absolute difference in adjusted mean TCRS between
320 the active and placebo groups being 1.¹⁵ In the present trial, the absolute differences met this
321 definition. The World Allergy Organization has suggested a minimum clinically relevant effect for
322 immunotherapy in general as being $\geq 20\%$ relative difference to placebo.²⁴ In the current trial, the
323 relative differences of TCRS from the placebo were 22% and 19% in the 10,000 and 20,000 JAU
324 groups, and 21% in the active all. The results of the primary endpoint assessments was also met
325 the FDA established efficacy criteria for SLIT products as a relative difference of $\geq 15\%$ in the
326 efficacy endpoint compared with placebo and a 95% CI upper limit of $\geq 10\%$.^{25,26} The clinical
327 relevance of the observed results is further supported by a significant improvement in JRQLQ for
328 both active groups compared to placebo and also by an increased number of days with no
329 rhinitis/conjunctivitis symptoms as well as a reduced number of days with severe symptoms (details
330 on the symptom relief evaluation and JRQLQ are available in the Results section with Table E7 and
331 E8 in the online repository).

332

333 As previously discussed the population in the current trial was characterized by a low use of allergy
334 pharmacotherapy, since subjects was instructed only to use pharmacotherapy if they had
335 intolerable symptoms. This was chosen to reflect the normal practice in Japan, where perennial AR
336 patients seldom use allergy pharmacotherapy on a regular basis but rather only when symptoms
337 are intolerable. Consequently it can be discussed if it would have been more relevant to use the AR
338 symptom score as primary endpoint in this trial. However, the total combined rhinitis score was
339 chosen based on current guidelines,^{20,24} and also to be able to compare with previous trials with the
340 SQ HDM SLIT-tablet. A change in AR symptom score as seen in the current trial can be a useful
341 indicator of how likely patients are to use allergy pharmacotherapy, since it has previously been
342 reported by Downie et al.²⁷ that an increase in the AR symptom score by 1 increased the likelihood
343 of a patient taking allergy pharmacotherapy by 25%.

344

345 A statistically significant difference in the AR symptoms score compared to placebo was first noted
346 at week 12, which is comparable to previous trials with the SQ HDM SLIT-tablet.^{15,28} Moreover, the
347 absolute differences between active and placebo groups tended to increase with increasing
348 treatment duration. This confirms that SQ HDM SLIT-tablet has an early onset of effect and provides
349 a year-round effect in the Japanese population which is crucial for treatment of a perennial allergy.

The potential for disease modification and long-term effect is a unique feature for AIT compared to pharmacotherapy. The post-treatment effect of the SQ HDM SLIT-tablet has not been investigated in this trial and remains to be confirmed. Post-treatment effect has previously been confirmed for the SQ grass SLIT-tablet in grass pollen allergic rhinoconjunctivitis.¹²

The trial enrolled both Japanese adult and adolescent subjects with HDM AR. The FAS included approximately 90 adolescents aged 12-17 years per treatment group (details on the demographics and baseline symptom scores are available in the Results section with Table E5 and E6 in the online repository). A *post-hoc* subgroup analysis on adults and adolescents demonstrated significant improvement in TCRS compared to placebo regardless of age group, suggesting similar efficacy in adults and adolescents. One important role of AIT in children and adolescents is to prevent the development of allergic asthma in subjects with AR. Jacobsen et al.¹⁰ reported the preventive effect of AIT on asthma in seasonal AR patients aged 6-14 years during a 3-year treatment period with a 7-year follow-up. Even though the efficacy of the SQ HDM SLIT-tablet in children below 12 years remains to be established, the results of the present study suggest that SQ HDM SLIT-tablet is a promising candidate to progress to the development of the pediatric use and eventually achieve a preventive effect at an early age.

As stated earlier, AIT in general and SCIT specifically has not been widely used in Japan due to safety concerns. However, the development of SLIT products with improved safety profiles has brought renewed attention to AIT in Japan. No serious ADRs or systemic allergic reactions were reported in this trial. The most commonly observed ADRs were mild local reactions such as mouth edema, oral pruritus, and throat irritation. In the current trial, an up-dosing scheme was chosen according to Japanese traditions. Up-dosing is mainly relevant with SCIT and have not been applied in the previous trials with the SQ HDM SLIT-tablet in Europe and US. The safety data from the Japanese population in the present trial is consistent with what has previously been observed with the SQ HDM SLIT-tablet²⁹ and confirms a safety and tolerability profile compatible with at-home administration, provided that the first dose is tolerated under medical supervision. The results also showed that the safety profile was similar between both adult and adolescent populations. The similar safety profiles in the previous and present trials show that with a regimen where patients are started on maintenance dose from the beginning of the treatment the SQ HDM SLIT-tablet is equally well tolerated compared to the up-dosing regimen used in the present trial.

For the development of the SQ HDM SLIT-tablet, the optimal dose needed to be established as the dose that provides the optimal balance between therapeutic effect and tolerability.³⁰ The phase II trial conducted in Europe showed a dose-response relationship for three doses, 1, 3 and 6

SQ-HDM.²¹ In the European SQ HDM SLIT-tablet pivotal trial conducted after confirming the dose-response,¹⁵ two doses, 6 SQ-HDM (10,000 JAU) and 12 SQ-HDM (20,000 JAU), were included. Clinical efficacy was demonstrated for both doses and both doses met the pre-defined criterion for clinical relevance. However, in the European population, 12 SQ-HDM (20,000 JAU) provided a more robust response with regard to key secondary endpoints and consequently 12 SQ-HDM (20,000 JAU) was chosen as the marketed dose in Europe. In the current study with the SQ HDM SLIT-tablet in a Japanese population comprising both adult and adolescent subjects, modest differences in the primary as well as the secondary endpoints were observed between the two doses. Consequently 10,000 JAU (6 SQ-HDM) was chosen as the marketed dose in Japan. Population-specific differences in the response to the treatment cannot be ruled out, but the similarity with regard to inclusion criteria and demographic characteristics of the European and Japanese trials together with comparable clinical responses indicate that both 10,000 JAU (6 SQ-HDM) and 20,000 JAU (12 SQ-HDM) may be effective and tolerated AR treatments in both populations.

In conclusion, the trial confirmed efficacy and favorable safety profile of both doses of the SQ HDM SLIT-tablet in Japanese adult and adolescent patients with moderate to severe HDM AR. These data confirm the previously reported European data and support the robust efficacy and safety

404 profile of the SQ HDM SLIT-tablet.

405

Acknowledgements:

The authors present this publication on behalf of all the involved investigators. The trial was funded by Torii and in this context the authors would like to thank the clinical trial team at Torii for clinical project management, operational oversight, quality control, safety monitoring, data management and statistics. Kazuhiro Okamiya, Torii, was responsible for medical writing, editorial, and journal submission assistance for this manuscript. The authors would like to thank Susanna Dahlgreen and Kaare Lund from ALK for reviewing the manuscript.

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506

507 **Tables**

508

509 **Table 1. Baseline characteristics and demography**

Treatment group	Placebo N=319	10,000 JAU N=313	20,000 JAU N=314	Active all N=627	Overall N=946
Age (y)					
Mean±SD	26.8 ± 11.7	27.2 ± 12.0	26.8 ± 12.1	27.0 ± 12.0	26.9 ± 11.9
Median [Min-Max]	25.0 [12-61]	25.0 [12-64]	25.0 [12-61]	25.0 [12-64]	25.0 [12-64]
Years with HDM AR					
Mean±SD	10.1 ± 8.7	10.0 ± 8.9	9.9 ± 9.0	10.0 ± 8.9	10.0 ± 8.8
Median [Min-Max]	8.0 [0-44]	7.0 [0-39]	7.0 [0-42]	7.0 [0-42]	7.0 [0-44]
Onset (y)					
Mean±SD	15.7 ± 12.1	16.1 ± 11.9	15.9 ± 12.2	16.0 ± 12.1	15.9 ± 12.1
Median [Min-Max]	11.0 [0-57]	12.0 [0-53]	11.0 [0-56]	11.0 [0-56]	11.0 [0-57]
Sex, no. (%)					
Male	132 (41.4)	156 (49.8)	145 (46.2)	301 (48.0)	433 (45.8)
Female	187 (58.6)	157 (50.2)	169 (53.8)	326 (52.0)	513 (54.2)
Specific IgE (kU/L), <i>D. farinae</i> , no. (%)					
< 17.5	114 (35.7)	117 (37.4)	114 (36.3)	231 (36.8)	345 (36.5)
17.5 ≤ to < 50	102 (32.0)	104 (33.2)	118 (37.6)	222 (35.4)	324 (34.2)
50 ≤ to < 100	63 (19.7)	52 (16.6)	36 (11.5)	88 (14.0)	151 (16.0)
100 ≤	40 (12.5)	40 (12.8)	46 (14.6)	86 (13.7)	126 (13.3)
Specific IgE (kU/L), <i>D. pteronyssinus</i> , no. (%)					
< 17.5	121 (37.9)	115 (36.7)	117 (37.3)	232 (37.0)	353 (37.3)
17.5 ≤ to < 50	102 (32.0)	104 (33.2)	118 (37.6)	222 (35.4)	324 (34.2)
50 ≤ to < 100	56 (17.6)	51 (16.3)	35 (11.1)	86 (13.7)	142 (15.0)
100 ≤	40 (12.5)	43 (13.7)	44 (14.0)	87 (13.9)	127 (13.4)
Sensitization status, no (%)					
Monosensitized	65 (20.4)	76 (24.3)	57 (18.2)	133 (21.2)	198 (20.9)
Polysensitized	254 (79.6)	237 (75.7)	257 (81.8)	494 (78.8)	748 (79.1)

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511

512 **Table 2. Analytical results on the primary endpoint (TCRS)**

Analysis set	Treatment group	N	Adjusted mean	Absolute difference from placebo (95% CI)	P value	Relative difference to placebo (95% CI)
Global null hypothesis (placebo = 10,000 JAU = 20,000 JAU)					<.001	-
FAS (LME)	Placebo	285	5.14	-	-	-
	10,000 JAU	285	3.99	1.15 (0.64 - 1.65)	<.001	22% (13% - 31%)
	20,000 JAU	281	4.14	0.99 (0.48 - 1.50)	<.001	19% (10% - 28%)
	Active all	566	4.07	1.07 (0.62 - 1.52)	<.001	21% (13% - 28%)
ITT (MMRM)	Placebo	317	5.15	-	-	-
	10,000 JAU	304	3.95	1.19 (0.70 - 1.69)	<.001	23% (14% - 31%)
	20,000 JAU	307	4.14	1.00 (0.51 - 1.49)	<.001	19% (10% - 28%)
	Active all	611	4.05	1.10 (0.68 - 1.52)	<.001	21% (14% - 28%)
PPS (LME)	Placebo	276	5.12	-	-	-
	10,000 JAU	279	3.98	1.15 (0.64 - 1.65)	<.001	22% (13% - 31%)
	20,000 JAU	274	4.16	0.96 (0.45 - 1.48)	<.001	19% (9% - 27%)
	Active all	553	4.07	1.06 (0.61 - 1.51)	<.001	21% (13% - 28%)

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514

Table 3. Summary of secondary endpoints in the last 8 weeks for symptom, medication and combined scores, and at week 52 for JRQLQ General State (FAS)

Secondary endpoint	Treatment group	N	Adjusted mean	Absolute difference from placebo (95% CI)		P value	Relative difference to placebo (95% CI)	
Key secondary endpoint (LME)								
	Global null hypothesis (placebo = 10,000 JAU = 20,000 JAU)					<.001	-	
AR symptom score	Placebo	285	4.75	-		-	-	
	10,000 JAU	285	3.69	1.05 (0.61 - 1.49)		<.001	22% (14% - 30%)	
	20,000 JAU	281	3.87	0.87 (0.43 - 1.32)		<.001	18% (10% - 27%)	
Other secondary endpoints (LME)								
AR medication score	Placebo	285	0.15	-		-	-	
	10,000 JAU	285	0.11	0.04 (-0.02 - 0.10)		.193	27% (-18% - 56%)	
	20,000 JAU	281	0.10	0.05 (-0.01 - 0.11)		.124	32% (-11% - 60%)	
Combined conjunctivitis score	Placebo	285	1.31	-		-	-	
	10,000 JAU	285	0.95	0.36 (0.15 - 0.57)		<.001	28% (13% - 40%)	
	20,000 JAU	281	0.97	0.34 (0.13 - 0.55)		.002	26% (11% - 39%)	
Conjunctivitis symptom score	Placebo	285	1.14	-		-	-	
	10,000 JAU	285	0.84	0.30 (0.12 - 0.48)		.001	26% (11% - 39%)	
	20,000 JAU	281	0.85	0.29 (0.10 - 0.47)		.002	25% (10% - 38%)	
Conjunctivitis medication score	Placebo	285	0.07	-		-	-	
	10,000 JAU	285	0.03	0.03 (0.01 - 0.06)		.012	48% (13% - 71%)	
	20,000 JAU	281	0.04	0.03 (0.00 - 0.05)		.040	41% (2% - 65%)	
JRQLQ General state	Evaluation index ^{*1}		0: Fine	1	2	3	4: Crying	P value ^{*2}
	Placebo	285	13 (4.6)	91 (31.9)	114 (40.0)	63 (22.1)	4 (1.4)	-
	10,000 JAU	285	28 (9.8)	109 (38.2)	98 (34.4)	43 (15.1)	7 (2.5)	.003
	20,000 JAU	281	32 (11.4)	105 (37.4)	90 (32.0)	49 (17.4)	5 (1.8)	.003

*1: N (%), *2: Wilcoxon rank sum test

519 **Table 4. Summary of safety**

Treatment group	Placebo N=319		10,000 JAU N=313		20,000 JAU N=314		Active all N=627		Overall N=946	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Serious adverse event (SAE)	3	(0.9)	5	(1.6)	5	(1.6)	10	(1.6)	13	(1.4)
Serious adverse drug reaction	-	-	-	-	-	-	-	-	-	-
Adverse event (AE)										
All AEs	256	(80.3)	280	(89.5)	284	(90.4)	564	(90.0)	820	(86.7)
Mild	232	(72.7)	252	(80.5)	254	(80.9)	506	(80.7)	738	(78.0)
Moderate	24	(7.5)	27	(8.6)	30	(9.6)	57	(9.1)	81	(8.6)
Severe	-	-	1	(0.3)	-	-	1	(0.2)	1	(0.1)
Adverse drug reaction (ADR)										
All ADRs	54	(16.9)	199	(63.6)	200	(63.7)	399	(63.6)	453	(47.9)
Mild	51	(16.0)	192	(61.3)	191	(60.8)	383	(61.1)	434	(45.9)
Moderate	3	(0.9)	7	(2.2)	9	(2.9)	16	(2.6)	19	(2.0)
Severe	-	-	-	-	-	-	-	-	-	-
Significant AEs										
Anaphylactic reaction	1 ^{*1}	(0.3)	-	-	-	-	-	-	1	(0.1)
Asthma	3	(0.9)	3	(1.0)	2	(0.6)	5	(0.8)	8	(0.8)
AEs leading to discontinuation ^{*2}	9	(2.8)	7	(2.2)	5	(1.6)	12	(1.9)	21	(2.2)
ADRs leading to interruption	5	(1.6)	14	(4.5)	14	(4.5)	28	(4.5)	33	(3.5)

*1: This subject is included in SAE.

*2: Including SAEs leading to discontinuation: 1 subject in the placebo group, 1 subject in the 20,000 JAU group;
subjects with asthma leading to discontinuation: 2 subjects in the placebo group, 3 subjects in the 10,000 JAU group.

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Figure Legends

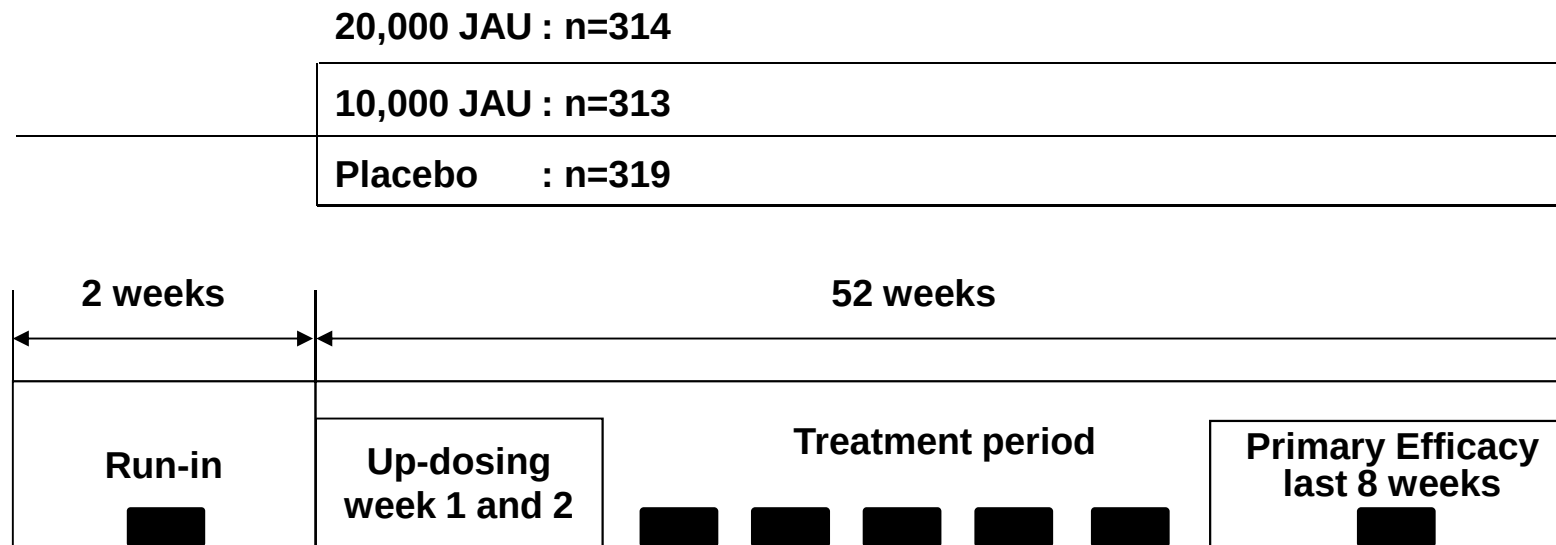
Figure 1: Trial design. Subjects were asked to follow a 2-step up-dosing regimen at the beginning of treatment period. The electronic diary collected 14 days of data during the run-in period and 5 times after up-dosing until the end of the primary evaluation period comprising the last 8 weeks of the treatment period. Black boxes represent electronic diary periods.

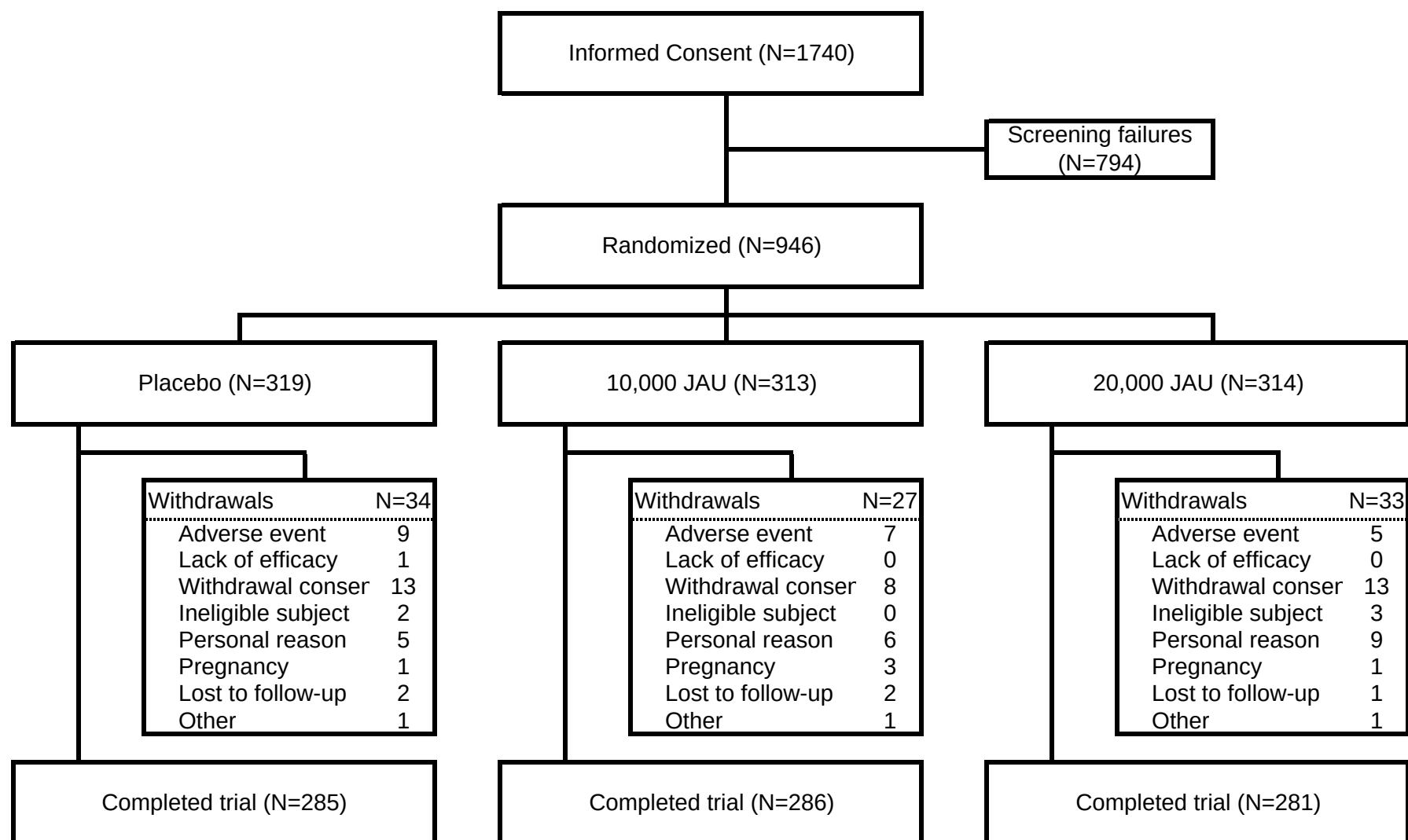
Figure 2: Subject disposition.

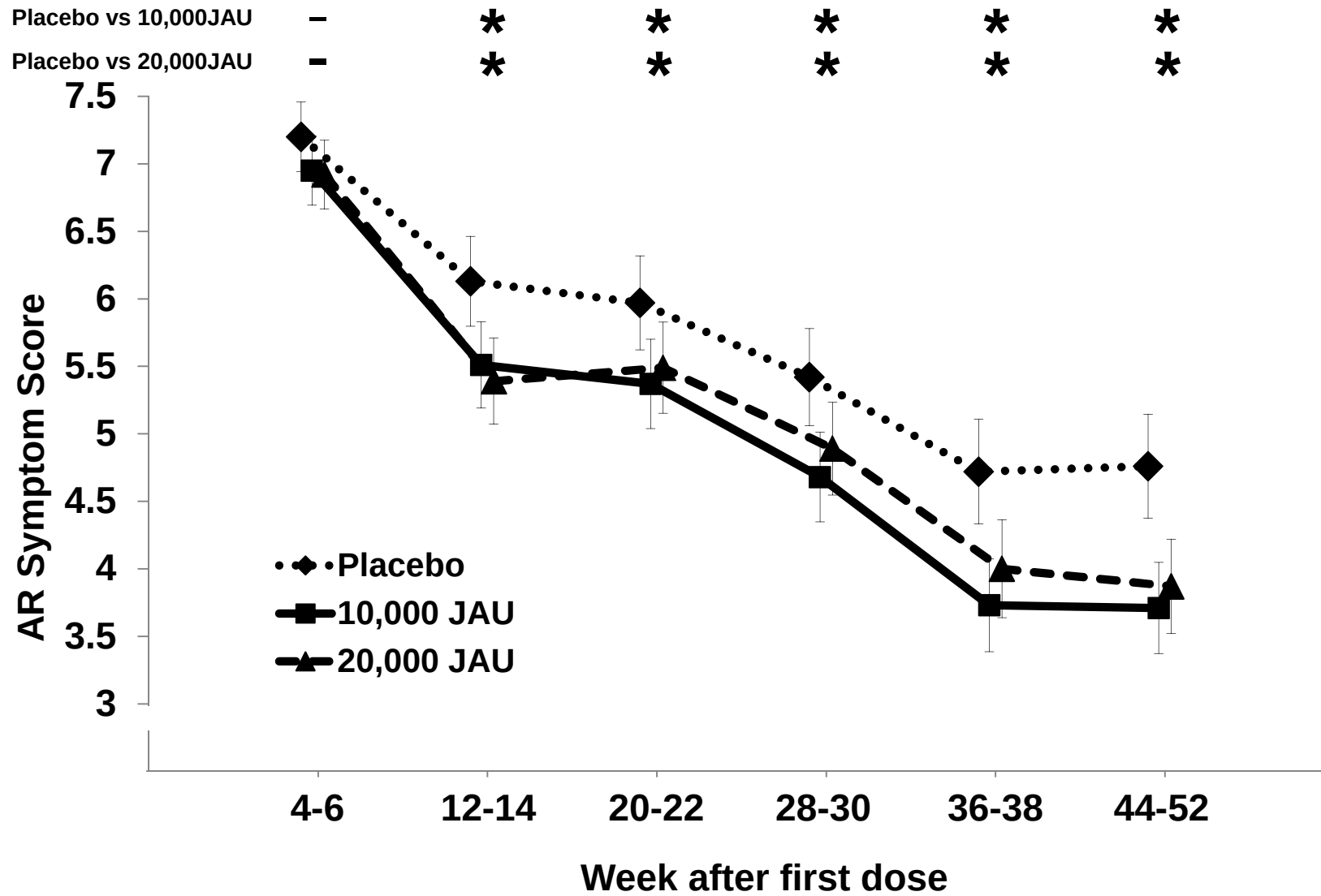
Figure 3: Adjusted means with 95% CIs of AR symptom score throughout the 52-week treatment period (primary evaluation period: week 44-52) and each symptom score during the primary evaluation period (week 44-52). Asterisks indicate a statistically significant difference from placebo. (FAS)

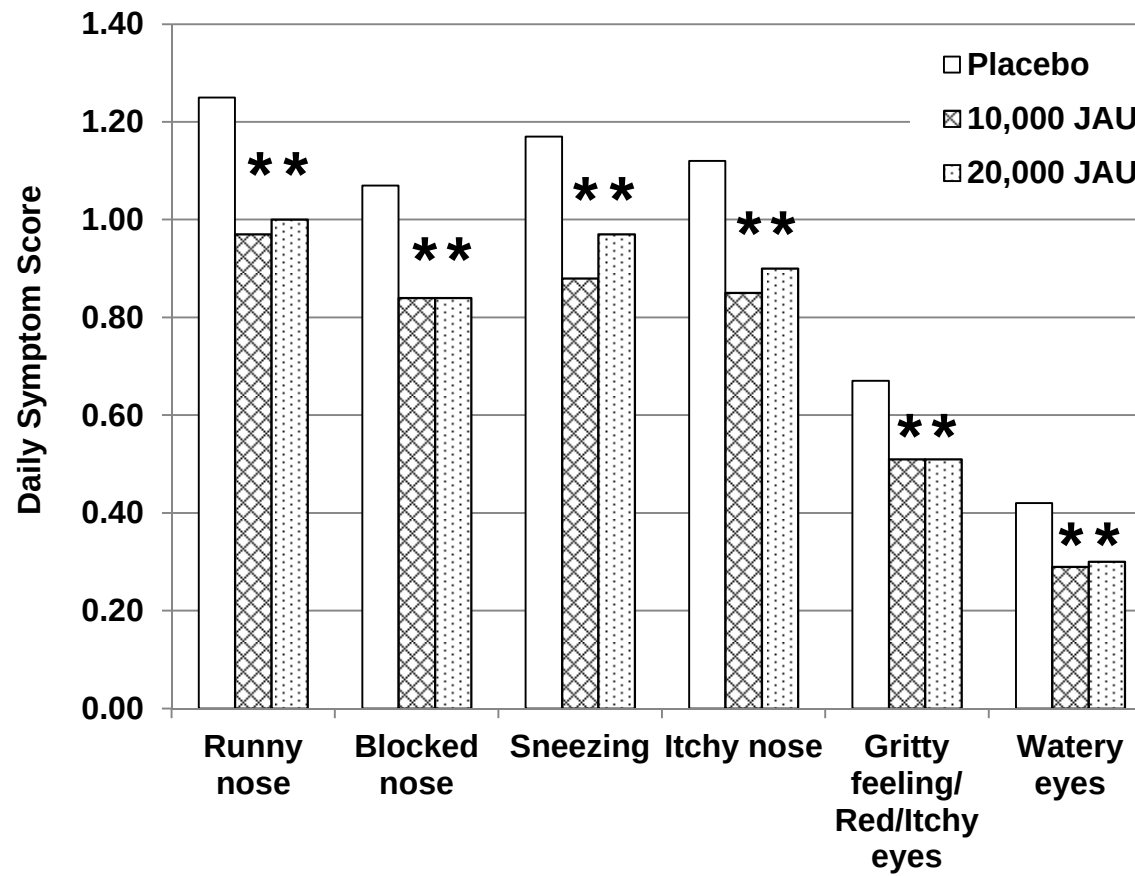
Figure 4: Comparison of TCRS between the adult (18-64) and adolescent (12-17) populations during the primary evaluation period (FAS) and incidence of adverse drug reactions with severity. A statistically significant difference from placebo in TCRS is indicated by the asterisks as confirmatory results (see Table 2) and in sharps for *post hoc* analysis.

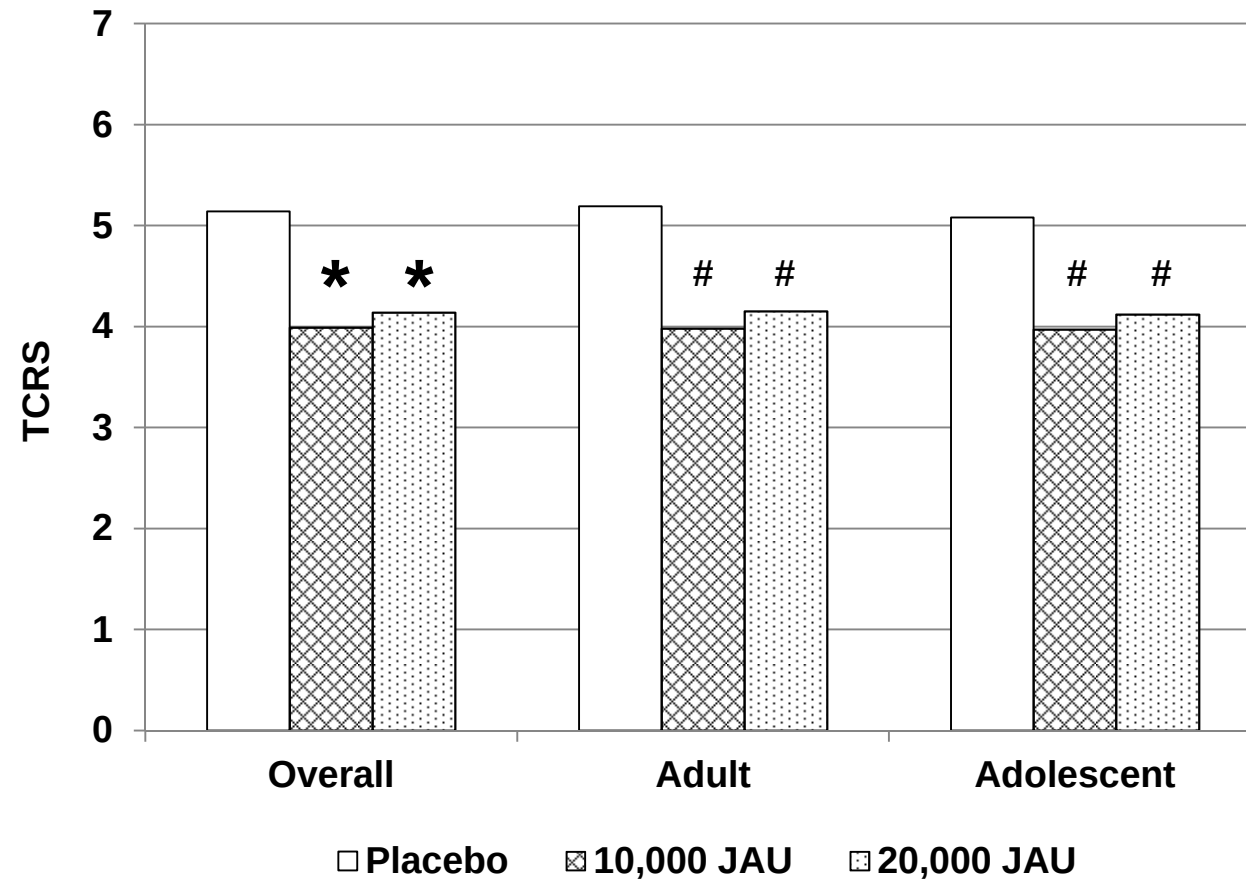
Trial Design

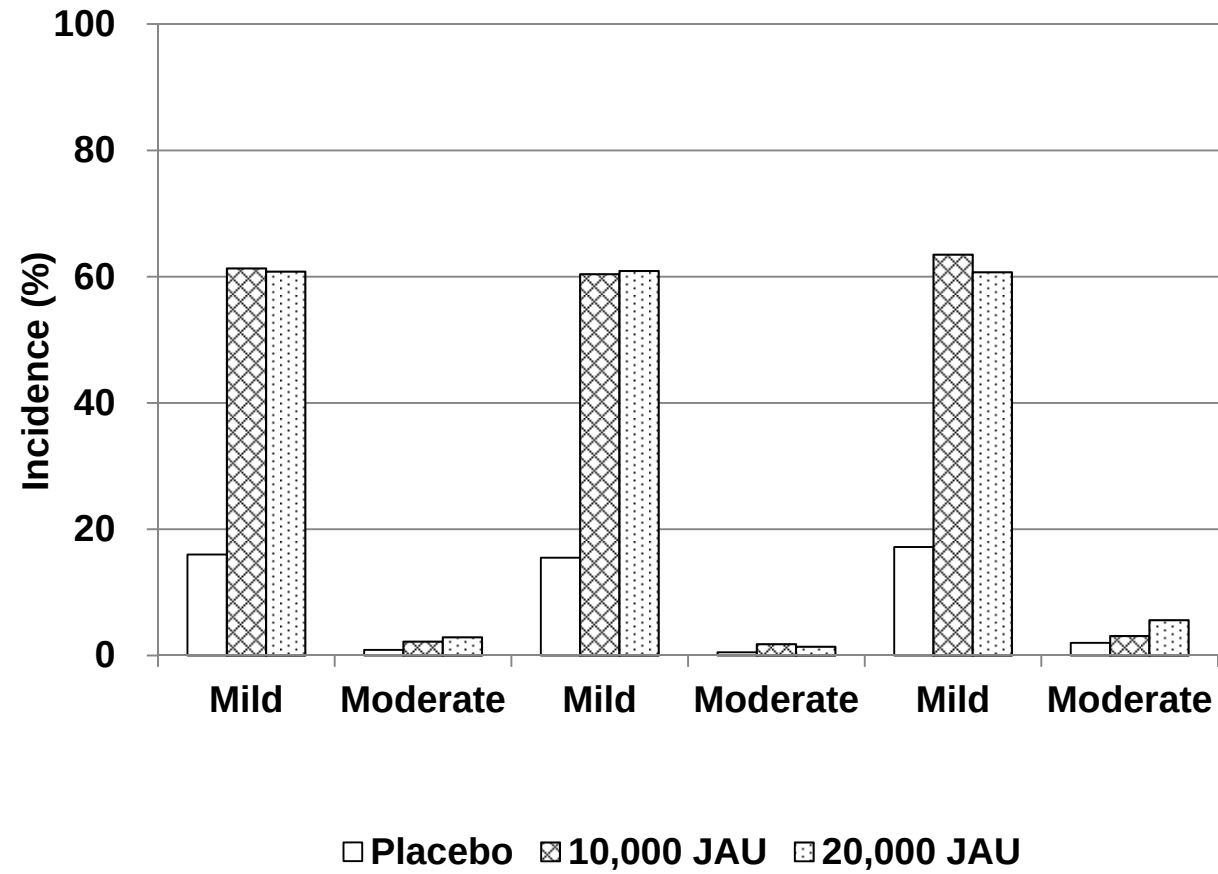












Supplementary text online repository

Efficacy and Safety of the SQ House Dust Mite SLIT-tablet in Japanese Adults and Adolescents with House Dust Mite-induced Allergic Rhinitis

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21

22 **Abbreviations**

23	AR	Allergic rhinitis
24	<i>D. farinae</i>	<i>Dermatophagoides farinae</i>
25	<i>D. pteronyssinus</i>	<i>Dermatophagoides pteronyssinus</i>
26	FAS	Full analysis set
27	HDM	House dust mite
28	ITT	Intention-to-treat
29	JAU	Japanese Allergy Unit
30	JRQLQ	Japanese Rhinoconjunctivitis Quality of Life Questionnaire
31	LME	Linear mixed effect
32	MMRM	Mixed model repeated measures
33	PPS	Per protocol analysis set
34	SLIT	Sublingual immunotherapy
35	TCSR	Total combined rhinitis score
36	WAO	The World Allergy Organization

37 **Methods**

38 *Population*

39 Main selection criteria

- 40 • Subjects 12-64 years of age, with a clinical history consistent with moderate to severe
41 persistent HDM allergic rhinitis without asthma for at least 1 year prior to informed consent,
42 with allergic rhinitis symptoms despite having received symptomatic treatment.
- 43 • Moderate to severe HDM allergic rhinitis symptoms during run-in period defined as a rhinitis
44 daily symptom score of at least 7 during at least 7 of the 14-day run-in period without any
45 symptomatic treatments.
- 46 • Presence of one or more of the following JRQLQ items due to HDM allergic rhinitis at the first
47 day of run-in period:
 - 48 1) Reduced productivity at work/home
 - 49 2) Impaired ability to read a book or newspaper
 - 50 3) Limitation of outdoor activities (e.g. sport, picnics)
 - 51 4) Limitation of ability to go out
 - 52 5) Hesitation visiting friend or relatives
 - 53 6) Reduced contact with friends or others by telephone or conversation
 - 54 7) Impaired sleeping
- 55 • Positive nasal provocation test response performed with house dust provocation kit.
- 56 • Positive specific IgE against *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and/or
57 *Dermatophagoides farinae* (*D. farinae*) (defined as HDM specific IgE ≥ 3.5 kU/L) without 50
58 kU/L $\leq$ of specific IgE in any of the following allergens: cedar, cypress, alder, cocksfoot,
59 ragweed, mugwort, Japanese hop, cockroach, Candida, Aspergillus, Alternaria, dog hair, or
60 cat hair.
- 61 • No clinically relevant history of symptomatic allergic rhinitis caused by any of the following
62 allergens if their specific IgEs are the range of $0.7 \leq$ to < 50 kU/L: cocksfoot, ragweed,
63 mugwort, Japanese hop, cockroach, Candida, Aspergillus, Alternaria, dog hair, or cat hair.
- 64 • Not constantly exposed to a dog and/or a cat (e.g. pet at home, working at a pet shop) even if
65 a patient has no symptoms with the range of $0.7 \leq$ to < 50 kU/L in the specific IgE of dog hair
66 or cat hair.

67

68 *Outcomes*

69 The construction of the scores used in the trial is shown in **Table E1** in accordance with information
70 obtained for symptom and medication scores of AR and conjunctivitis based on the **Table E2** and
71 **E3**. Maximum daily doses were 1 oral antihistamine tablet with a score of 4, 2 times of nasal
72 corticosteroid spray with a maximum score of 8 (a score of 4 per puff(s) regardless of one or both
73 nostrils), and 4 times of antihistamine eye drops with a maximum score of 6 (a score of 1.5 per
74 drop(s) regardless of one or both eyes).

75

76 *Sample size*

77 The power calculation was based on data from a previous trial of the SQ HDM SLIT-tablet.^{E1} The
78 observed mean of the TCRS for placebo was 4.9, and the coefficient of variation (SD/mean) was
79 0.82. Based on these assumptions, the relative differences between the active drugs, 10,000 JAU
80 and 20,000 JAU, and placebo used in the power calculations were 20% and 25%, respectively.

81 These correspond to the WAO recommendation^{E2} that the minimum difference with clinical
82 significance between active and placebo groups should be 20% for the primary endpoint.

83 In a simulation with SAS under the abovementioned hypothesis, a power of approximately 92% was
84 obtained, which rejects the comprehensive hypothesis that there is no difference between treatment

groups based on the F test with a significance level of 5% in the analysis population of 270 subjects in a treatment group of 300 subjects with a 10% discontinuation rate. This means the difference between 10,000- and 20,000-JAU combined and placebo groups can be detected with a power of approximately 92%. Further power calculations to detect a difference from placebo for 10,000 JAU and 20,000 JAU are presented in **Table E4**.

Statistical methodology

All statistical tests were performed with SAS version 9.3 software (SAS Institute, Cary, NC) with a 5% significance level, and all tests and 95% CIs were 2-sided.

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

The primary efficacy analysis was based on a linear mixed effect (LME) model adopting the AR symptom score at baseline and the treatment group as fixed effects and clinical site as a random effect with FAS. Square root transformation was performed for TCRS (primary endpoint) and AR symptom score (key secondary endpoint) in the primary evaluation period as a dependent variable and the AR symptom score at baseline as a covariate. The primary outcome was the pairwise comparison between treatment groups by using a t-test in the LME model. Confidence intervals for

the ratios of the adjusted mean values between treatment groups were calculated using Fieller's theorem.^{E3} Back transformation was performed for output results of the square root of the variables to indicate the adjusted mean values, difference in the adjusted mean values between treatment groups, confidence intervals, the ratios of the adjusted mean values between treatment groups, and confidence intervals.

The Fisher least significant difference procedure^{E4} was used to control for multiplicity in the primary efficacy analysis. By using an F-test in the LME model, the first hypothesis to be tested was the global hypothesis of no difference in means between the 3 groups: placebo, 10,000 JAU, and 20,000 JAU. If and only if this global hypothesis was rejected ($P < .05$), all pairwise comparisons between treatment groups were performed (20,000 JAU vs placebo, 10,000 JAU vs placebo, and 20,000 JAU vs 10,000 JAU).

Additional analyses included the same LME model on the PPS and mixed model repeated measures (MMRM) method on ITT. For MMRM, the variance structure was unstructured correlation (UN), and the computation method for covariance matrices of fixed effects was robust (sandwich) covariance matrix estimator.

Other symptom and medication scores were analyzed by the same LME model with appropriate changes of dependent variables and covariates. Intergroup paired comparison evaluated by logistic regression was performed for symptom-free and -severe day evaluation with presence or absence

of the relevant days in the primary evaluation period (0, 1 variable) as a dependent variable and the square rooted AR symptom score at baseline and the treatment group as fixed effects. JRQLQ was analyzed by the Wilcoxon rank sum test.

Results

Population

Table E5 shows the stratified demographic data divided into adult and adolescent populations in the FAS analysis set with baseline symptom scores (**Table E6**). Although conjunctivitis symptom scores in adolescents are a little lower than that for adults, there is no difference in rhinitis scores between these 2 groups.

Symptom relief secondary endpoint

Two additional secondary endpoints were prespecified. They were the proportion of symptom-free and symptom-severe days during the primary evaluation period. A symptom-free day for AR was defined as a day of AR symptom score of 0 with no use of oral antihistamine and nasal steroid. In contrast, a symptom-severe day was counted regardless of use of allergy pharmacotherapy. Like AR, a day of conjunctivitis symptom score of 0 with no use of oral and ocular antihistamines was handled as a symptom-free day. A symptom-severe day was counted the same way as AR. All

evaluated days were statistically significantly different from placebo (**Table E7**).

JRQLQ

JRQLQ was assessed at randomization, week 4, 28, 44, and 52. Four AR and 2 conjunctivitis symptoms were assessed as the worst symptoms during 1-2 weeks before the site visit based on subject recall. All symptoms improved in a treatment duration-dependent manner, and all changes in symptoms in both active doses reached statistical significance compared with placebo (**Table E8**).

Table E1. Construction of scores used in the trial

	TCRS	AR symptom score	AR medication score	Total combined conjunctivitis score	Conjunctivitis symptom score	Conjunctivitis medication score
Runny nose	0-3	0-3				
Blocked nose	0-3	0-3				
Sneezing	0-3	0-3				
Itchy nose	0-3	0-3				
Gritty feeling/ Red/Itchy eyes				0-3	0-3	
Watery eyes				0-3	0-3	
Oral antihistamine	0-4		0-4	0-2		0-2
Nasal steroid	0-8		0-8			
Ocular antihistamine				0-6		0-6
Total	0-24	0-12	0-12	0-14	0-6	0-8

Table E2. Symptom evaluation and score

Symptoms	Severity and score
Rhinitis • Runny nose • Blocked nose • Sneezing • Itchy nose	0: Absent symptoms (<i>no sign/symptom evident</i>)
	1: Mild symptoms (<i>sign/symptom clearly present, but minimal awareness; easily tolerated</i>)
	2: Moderate symptoms (<i>definite awareness of sign/symptom that is bothersome but tolerable</i>)
	3: Severe symptoms (<i>sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping</i>)
Conjunctivitis • Gritty feeling/Red/Itchy eyes • Watery eyes	

Table E3. Allergy pharmacotherapy and score

Allergy pharmacotherapy	Score	Maximum Daily Score**
Rhinitis		
Oral antihistamine	4	4
Nasal steroid	4*	8
Total maximum daily score		12
Conjunctivitis		
Oral antihistamine	2	2
Ocular antihistamine	1.5*	6
Total maximum daily score		8

* Use of one side or both sides is counted as the same points (considered as one-time use).

** Oral antihistamine: Loratadine tablet 10 mg once daily, Nasal steroid: Fluticasone propionate nasal solution 50 µg metered spray and 25 µg metered spray for pediatric use twice daily each, Ocular antihistamine: Olopatadine hydrochloride ophthalmic solution 0.1% 4 times per day

Table E4. Power for statistical analysis

Hypotheses to be rejected	Difference (%) from placebo to be detected		N total	Power to reject
	10,000 JAU	20,000 JAU		
$H_{0,1}$: placebo=10,000 JAU=20,000 JAU	20%	25%	900	92%
$H_{0,1}$: placebo=10,000 JAU=20,000 JAU and $H_{0,2}$: placebo=20,000 JAU	20%	25%	900	91%
$H_{0,1}$: placebo=10,000 JAU=20,000 JAU and $H_{0,3}$: placebo=10,000 JAU	20%	25%	900	79%
$H_{0,1}$: placebo=10,000 JAU=20,000 JAU and $H_{0,2}$: placebo=20,000 JAU and $H_{0,3}$: placebo=10,000 JAU	20%	25%	900	77%

161 **Table E5. Comparison of demographics in adults and adolescents (FAS)**

Item		Adults (18 to 64)			Adolescents (12 to 17)		
		Placebo	10,000 JAU	20,000 JAU	Placebo	10,000 JAU	20,000 JAU
		N=193	N=198	N=182	N=92	N=87	N=99
Sex	Male	68 (35%)	82 (41%)	66 (36%)	53 (58%)	57 (66%)	65 (66%)
	Female	125 (65%)	116 (59%)	116 (64%)	39 (42%)	30 (35%)	34 (34%)
Specific IgE (kU/L) <i>D. farinae</i>	< 17.5	92 (48%)	96 (49%)	88 (48%)	16 (17%)	10 (12%)	13 (13%)
	17.5 ≤ to < 50	64 (33%)	64 (32%)	65 (36%)	27 (29%)	32 (37%)	41 (41%)
	50 ≤ to < 100	25 (13%)	28 (14%)	18 (10%)	27 (29%)	21 (24%)	14 (14%)
	100 ≤	12 (6%)	10 (5%)	11 (6%)	22 (24%)	24 (28%)	31 (31%)
Specific IgE (kU/L) <i>D. pteronyssinus</i>	< 17.5	93 (48%)	92 (47%)	89 (49%)	20 (22%)	12 (14%)	13 (13%)
	17.5 ≤ to < 50	63 (33%)	68 (34%)	64 (35%)	24 (26%)	28 (32%)	44 (44%)
	50 ≤ to < 100	25 (13%)	26 (13%)	17 (9%)	25 (27%)	22 (25%)	14 (14%)
	100 ≤	12 (6%)	12 (6%)	12 (7%)	23 (25%)	25 (29%)	28 (28%)
Multiple sensitization	Mono sensitization	36 (19%)	50 (25%)	37 (20%)	21 (23%)	20 (23%)	18 (18%)
	1 - 2	81 (42%)	68 (34%)	87 (48%)	38 (41%)	43 (49%)	36 (36%)
	3 - 4	45 (23%)	51 (26%)	35 (19%)	21 (23%)	10 (12%)	32 (32%)
	5 - 6	14 (7%)	18 (9%)	9 (5%)	10 (11%)	8 (9%)	7 (7%)
	7 - 8	10 (5%)	9 (5%)	7 (4%)	1 (1%)	3 (3%)	2 (2%)
	≥9	7 (4%)	2 (1%)	7 (4%)	1 (1%)	3 (3%)	4 (4%)

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163 **Table E6. Comparison of baseline symptom scores in adults and adolescents (FAS)**

Symptom score	Adults (18 to 64)			Adolescents (12 to 17)		
	Placebo	10,000 JAU	20,000 JAU	Placebo	10,000 JAU	20,000 JAU
	N=193	N=198	N=182	N=92	N=87	N=99
Runny nose	2.16 ± 0.40 2.07 [1.3-3.0]	2.24 ± 0.38 2.21 [1.3-3.0]	2.20 ± 0.36 2.14 [1.2-3.0]	2.27 ± 0.37 2.21 [1.5-3.0]	2.24 ± 0.39 2.21 [1.3-3.0]	2.26 ± 0.45 2.23 [0.9-3.0]
Blocked nose	2.03 ± 0.47 2.00 [0.6-3.0]	2.10 ± 0.53 2.07 [0.9-3.0]	2.03 ± 0.50 2.00 [0.1-3.0]	2.15 ± 0.49 2.07 [0.9-3.0]	2.11 ± 0.46 2.00 [1.0-3.0]	2.07 ± 0.58 2.00 [0.3-3.0]
Sneezing	2.08 ± 0.46 2.00 [0.9-3.0]	2.11 ± 0.48 2.07 [0.6-3.0]	2.12 ± 0.43 2.04 [0.6-3.0]	2.07 ± 0.51 2.07 [0.7-3.0]	2.08 ± 0.45 2.00 [0.9-3.0]	2.20 ± 0.45 2.14 [1.0-3.0]
Itchy nose	2.09 ± 0.44 2.00 [0.8-3.0]	2.12 ± 0.48 2.07 [0.1-3.0]	2.11 ± 0.43 2.07 [0.8-3.0]	2.05 ± 0.47 2.07 [1.0-3.0]	1.99 ± 0.45 2.00 [0.9-3.0]	2.01 ± 0.49 2.00 [0.3-3.0]
AR symptom score	8.36 ± 1.35 8.29 [4.9-11.6]	8.58 ± 1.29 8.39 [5.8-12.0]	8.46 ± 1.23 8.29 [5.6-11.8]	8.55 ± 1.28 8.39 [6.2-11.7]	8.43 ± 1.24 8.21 [5.7-11.1]	8.54 ± 1.34 8.50 [6.3-11.5]
Gritty feeling/ Red/Itchy eyes	1.49 ± 0.66 1.50 [0.0-3.0]	1.55 ± 0.70 1.57 [0.0-3.0]	1.53 ± 0.65 1.57 [0.0-3.0]	1.49 ± 0.76 1.54 [0.0-3.0]	1.37 ± 0.75 1.50 [0.0-2.7]	1.37 ± 0.74 1.36 [0.0-3.0]
Watery eyes	1.21 ± 0.70 1.14 [0.0-2.9]	1.24 ± 0.76 1.29 [0.0-2.9]	1.24 ± 0.72 1.25 [0.0-2.8]	1.09 ± 0.77 1.07 [0.0-2.9]	1.05 ± 0.73 1.00 [0.0-2.5]	1.05 ± 0.74 1.00 [0.0-2.6]
Conjunctivitis symptom score	2.70 ± 1.30 2.79 [0.0-5.9]	2.78 ± 1.37 2.86 [0.0-5.9]	2.76 ± 1.32 2.71 [0.0-5.8]	2.58 ± 1.44 2.64 [0.0-5.9]	2.42 ± 1.40 2.57 [0.0-5.0]	2.42 ± 1.38 2.43 [0.0-5.6]

Mean ± SD, Median [Min-Max]

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165 **Table E7. Symptom relief evaluation at the end of treatment period**

Endpoint	Symptom	Treatment group	N	Logistic regression ^{*1}		
				Probability ^{*2} (%)	against Placebo	
					Odds ratio [95% CI]	p value
Symptom-free days	AR	Placebo	285	26.0	-	-
		10,000 JAU	285	39.0	1.82 [1.27; 2.60]	.001
		20,000 JAU	281	33.9	1.46 [1.02; 2.10]	.041
	Conjunctivitis	Placebo	285	66.8	-	-
		10,000 JAU	285	75.3	1.52 [1.05; 2.20]	.028
		20,000 JAU	281	75.3	1.52 [1.04; 2.21]	.029
Symptom-severe days	AR	Placebo	285	25.9	-	-
		10,000 JAU	285	36.8	1.66 [1.16; 2.38]	.006
		20,000 JAU	281	34.8	1.52 [1.06; 2.19]	.023
	Conjunctivitis	Placebo	285	66.8	-	-
		10,000 JAU	285	76.3	1.60 [1.10; 2.33]	.014
		20,000 JAU	281	75.3	1.52 [1.04; 2.20]	.029

*1: Fixed effect: Treatment groups

*2: Subjects with at least 1 day of "symptom-free days", or with no "symptom-severe days" during the primary evaluation period

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167 **Table E8. Symptom assessment in JRQLQ during the course of the trial**

Treatment group	Symptom	p value (Wilcoxon rank sum test against Placebo)					
		Randomization	Week 4	Week 28	Week 44	Week 52	
10,000 JAU	AR	Runny nose	.111	.969	.656	.021	.039
		Blocked nose	.475	.371	.305	.041	.007
		Sneezing	.100	.090	.650	.002	.012
		Itchy nose	.836	.354	.023	.012	<.001
	Conjunctivitis	Itchy eyes	.302	.568	.045	.063	.007
		Watery eyes	.193	.270	.102	.028	.037
20,000 JAU	AR	Runny nose	.349	.478	.071	.022	.001
		Blocked nose	.481	.090	.016	.010	.001
		Sneezing	.187	.475	.346	.051	.014
		Itchy nose	.548	.168	.004	.022	<.001
	Conjunctivitis	Itchy eyes	.447	.548	.009	.003	.007
		Watery eyes	.432	.354	.055	.016	.021

Each symptom was assessed according to a 5-grade scale as follows: 0: No symptoms, 1: Mild, 2: Moderate, 3: Severe, 4: Very severe. White columns indicate statistically significant from placebo.

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