

Original Article

Efficacy and Safety of HDM SLIT Tablet in Japanese Adults with Allergic Asthma

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What is already known about this topic? According to the Global Initiative for Asthma global strategy for asthma management and prevention, sublingual immunotherapy is a treatment option for adults with house dust mite allergic asthma.

What does this article add to our knowledge? This trial did not meet the primary efficacy end point. However, post hoc analysis shows that the treatment was potentially efficacious in those who required short-acting β_2 -agonists to control their symptoms.

How does this study impact current management guidelines? The post hoc analysis of the Japanese patients who required short-acting β_2 -agonists during the baseline period supports European data on the efficacy of the standardized quality house dust mite sublingual immunotherapy tablet in patients suffering from house dust mite allergic asthma.

BACKGROUND: The standardized quality (SQ) house dust mite (HDM) sublingual immunotherapy (SLIT) tablet has demonstrated efficacy and safety for allergic asthma (AA) in European trials.

OBJECTIVE: To evaluate the efficacy and safety of SQ HDM SLIT tablet treatment for up to 19 months in Japanese adults with AA.

METHODS: In this randomized, double-blind, placebo-controlled trial, patients aged 18 to 64 years with AA were randomly assigned (1:1:1) to SQ HDM SLIT doses of 10,000 or 20,000 Japanese Allergy Unit or placebo. Subjects had Asthma Control Questionnaire score of 1.0 to 1.5 and daily inhaled corticosteroid use of 200 to 400 μ g of fluticasone propionate at randomization. The primary end point was the time from

randomization to the first asthma exacerbation as the inhaled corticosteroid dose was being reduced.

RESULTS: Of the 826 randomized subjects, 693 (84%) completed the trial. No statistically significant differences between the active groups and the placebo group were observed for the primary or any other efficacy end points. However, post hoc analysis indicated a significant difference between the 20,000 Japanese Allergy Unit and placebo groups among subjects who used a short-acting β_2 -agonist during the baseline period (hazard ratio, 0.70; 95% CI, 0.48-1.00; $P = .04997$). No deaths or anaphylactic reactions were reported. Most adverse events were mild to moderate in severity.

CONCLUSIONS: The trial demonstrated a favorable safety profile of the SQ HDM SLIT tablet in Japanese adult patients with AA. The treatment appeared to be efficacious in patients requiring rescue medication (ie, short-acting β_2 -agonist) at baseline in the efficacy assessment using asthma exacerbation during inhaled corticosteroid reduction (JapicCTI number 121847). © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Allergy immunotherapy; Sublingual immunotherapy; House dust mite; Allergy; Allergic asthma; Asthma exacerbation; SLIT tablet; Inhaled corticosteroid

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INTRODUCTION

Dermatophagoides farinae and *Dermatophagoides pteronyssinus*, 2 species of house dust mites (HDMs), are among the most common indoor allergens. They are considered to be a principal cause of allergic diseases such as asthma, rhinitis, and atopic dermatitis. In particular, sensitization to HDMs is a major risk factor for the development of asthma,¹ increases bronchial hypersensitivity to a greater degree than does sensitization to pollen,² and is related to asthma severity.³

Abbreviations used

AA- Allergic asthma
 ACQ- Asthma Control Questionnaire
 e-diary- Electronic diary
 FAS- Full analysis set
 GINA- Global Initiative for Asthma
 HDM- House dust mite
 ICS- Inhaled corticosteroid
 IMP- Investigational medicinal product
 JAU- Japanese Allergy Unit
 SABA- Short-acting β_2 -agonist
 SLIT- Sublingual immunotherapy
 SQ- Standardized quality

Since the advent of inhaled corticosteroids (ICSs) to treat asthma,⁴ the number of deaths from the disease has decreased,⁵ even as the prevalence of bronchial asthma is increasing in many countries.^{6,7} In addition to ICSs, other agents such as long-acting β_2 -agonists, leukotriene receptor antagonists, and biologics provide control even in the most severe cases. Although these drugs are effective, treatment is required semipermanently because asthma symptoms will recur if the pharmacotherapies are discontinued.

Allergy immunotherapy may provide a disease-modifying effect and has been shown to result in a decrease in the amount and frequency of pharmacotherapy use and to maintain treatment effects posttreatment.⁸⁻¹¹ One such product is the standardized quality (SQ) HDM sublingual immunotherapy (SLIT) tablet (MITICURE, Torii, Japan/ACARIZAX, ALK, Hørsholm, Denmark), formulated as a rapidly dissolving oral lyophilisate for sublingual administration.^{12,13} On the basis of confirmatory results of clinical trials in patients with HDM allergic rhinitis,¹⁴⁻¹⁷ the SQ HDM SLIT tablet has been used in Europe, Asia, North America, and Oceania. A large trial conducted in Europe among patients with HDM allergic asthma (AA) also proved the efficacy and safety in HDM AA.¹⁸ On the basis of these results, SLIT has been recommended as a treatment option for patients with HDM AA in steps 3 and 4 in the latest Global Initiative for Asthma (GINA) global strategy for asthma management and prevention.⁶ The present trial was conducted for investigating the efficacy and safety of the SQ HDM SLIT tablet in Japanese adults with HDM AA. This is the first publication on the primary results obtained from this trial.

METHODS**Trial design**

This randomized, double-blind, placebo-controlled trial was conducted at 124 sites in Japan from June 2012 to May 2014 (JapicCTI number 121847). The trial complied with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the institutional review board at each clinical site. Written informed consent was obtained from all subjects and legal representatives of underage subjects. The sponsors, subjects and their legal representatives, investigators, and trial personnel were blinded to the treatment until database lock.

The trial design is shown in Figure 1. After giving informed consent, all subjects were required to switch their usual asthma treatment to fluticasone propionate and short-acting β_2 -agonist (SABA) as required before screening. Electronic diary (e-diary) recordings, including asthma symptoms (wheezing, coughing, shortness of breath, chest

tightness, and nocturnal awakening); medication use; and peak expiratory flow of the last 2 weeks of period 1 (baseline period) served as each subject's individual baseline. Eligible subjects were randomly assigned (1:1:1) to daily treatment with placebo or the SQ HDM SLIT tablet at a dose of 10,000 Japanese Allergy Unit (JAU)¹⁹ or 20,000 JAU in addition to the required ICS and SABA. Randomization was performed in blocks of 3 comprising the 3 different treatments using an interactive Web response system programmed by Bell Medical Solutions, Inc (Tokyo, Japan). As in the Japanese HDM rhinitis trial of the SQ HDM SLIT tablet,¹⁴ a 2-step up dosing regimen was used. On the basis of the results of European and Japanese phase 1 trials,^{20,21} the 10,000 JAU and 20,000 JAU were chosen as the active groups. The duration of period 2 varied from 7 to 13 months depending on the date of randomization. All subjects with Asthma Control Questionnaire (ACQ) scores of 1.5 or less at the first visit to the ICS reduction period (period 3) proceeded to period 3 on a fixed date in September 2013, and those with ACQ scores of more than 1.5 would not proceed to period 3 to avoid ICS reduction in subjects with uncontrolled asthma. During period 3, daily ICS dose was reduced by 50% for the first 3 months and subsequently withdrawn completely for those subjects who did not experience asthma exacerbation. Subjects recorded in the e-diary twice daily during period 1, the last 4 weeks of period 2, and period 3.

The SQ HDM SLIT tablet is a fast-dissolving freeze-dried tablet with a 1:1 mixture of allergen extracts of *D pteronyssinus* and *D farinae*. 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.^{12,13} A nominal strength of 10,000 JAU has the same potency as 6 SQ-HDM (SQ-HDM is the unitage used in Europe and the United States), with 20,000 JAU equivalent to 12 SQ-HDM. The placebo and active products were similar in appearance, smell, and taste. The first dose was given at the clinical site, followed by a 30-minute period of observation under medical supervision. ICS, SABA, and oral corticosteroid as rescue medications were provided by the trial sponsor to the subjects.

Trial population

Subjects were recruited between July 2012 and January 2013. Eligible subjects were diagnosed with asthma according to Japanese guidelines for adult asthma between 18 and 64 years and tested positive for skin prick test or scratch test to HDM; a specific serum IgE level of greater than or equal to 3.5 kU/L against *D pteronyssinus*, *D farinae*, or both; a documented reversible airway obstruction and more than 6 months of AA treated at least with ICS; AA not well controlled by ICS (equivalent to fluticasone propionate, 200-400 μ g), including combination products with long-acting β_2 -agonist at randomization judged by ACQ score of 1.0 to 1.5; and FEV₁ of more than 70% of predicted value at randomization. Hospitalization due to an asthma exacerbation within 3 months before randomization, a clinical history of systemic diseases that affect the immune system (eg, autoimmune disease, immune complex disease, and immunodeficiency), and other respiratory diseases (eg, chronic obstructive pulmonary disease) that could affect the efficacy and safety evaluation were excluded. Subjects with a relevant clinical history of perennial AA or rhinitis due to regular exposure to antigens other than HDM were also excluded.

Details of the selection criteria are available in the Methods section in this article's Online Repository at www.jaci-inpractice.org.

Assessment

The primary end point was the time from randomization to the first moderate or severe asthma exacerbation during period 3. The

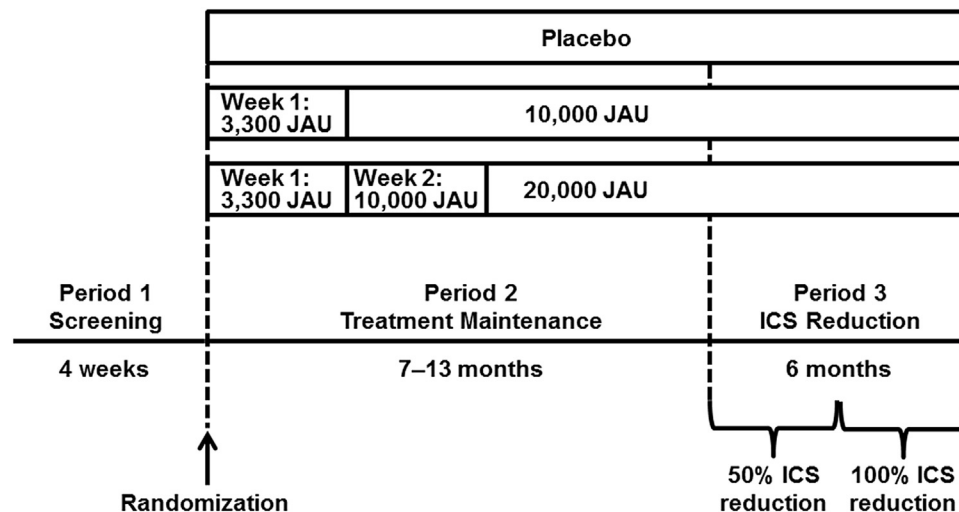


FIGURE 1. Trial design. Subjects were asked to follow a 2-step increase in the SQ HDM SLIT-tablet dose at the beginning of the treatment period. All subjects entering period 3 reduced daily ICS use by 50% for 3 months. Those who had no asthma exacerbations in those 3 months completely discontinued their ICS.

definition of an exacerbation was similar to that in the European trial¹⁸ and based on the American Thoracic Society and the European Respiratory Society recommendations.^{22,23} A moderate asthma exacerbation was defined as (1) nocturnal awakening(s) due to asthma requiring a SABA for at least 2 consecutive nights or an increase of at least 0.75 points in the daily symptom score from the baseline value on at least 2 consecutive days, (2) an increase from baseline in SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day), (3) a 20% or more decrease in peak expiratory flow from baseline on at least 2 consecutive mornings or evenings or a 20% or more decrease in FEV₁ from baseline, or (4) a visit to the emergency department or an unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids. A severe asthma exacerbation was defined as (1) a requirement for systemic corticosteroids for the treatment of asthma symptoms or (2) an emergency department visit due to asthma requiring systemic corticosteroids or hospitalization due to asthma (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). A key secondary end point was the time from the start of period 3 to the first moderate or severe asthma exacerbation. Although there were 10 other secondary end points primarily associated with asthma symptoms, this article mainly focuses on post hoc analyses of the primary and key secondary end points.

HDM-specific IgE and IgG₄ levels were measured to confirm the specific immunologic response.

The safety profile was assessed by recording adverse events during treatment.

Statistical analysis

Sample size calculation was based on the European trial of the SQ HDM SLIT tablet in HDM AA.²⁴ It was assumed that approximately 65% of subjects in the placebo group would experience an asthma exacerbation during period 3. We designed the trial to determine an absolute difference of 13% and a hazard ratio of 0.70 between the 10,000 JAU and placebo groups and a difference of 16% and a hazard ratio of 0.64 between the 20,000 JAU and placebo groups. Using simulation with log-rank test analysis from randomization to asthma exacerbation during period 3 and

estimating 10% and 4% discontinuation rates during periods 2 and 3, respectively, including 300 subjects in each group had an approximately 82% power to detect all differences among 3 groups between the 10,000 JAU and placebo groups, and between the 20,000 JAU and placebo groups. The primary analysis population, that is, the full analysis set (FAS), included all randomized subjects. Efficacy for the primary end point was analyzed with the log-rank test. The key secondary end point was analyzed with a Cox proportional hazards regression model adopting the treatment group as a fixed effect in the FAS population with multiple imputations of missing data. Multiplicity was controlled by a closed testing procedure that performed sequential testing starting from a high dose. Details on sample size calculations and statistical analysis are available in the Methods section and Table E2 in this article's Online Repository at www.jaci-inpractice.org.

RESULTS Population

The disposition of trial subjects is shown in Figure 2. Informed consent was obtained from 1335 patients, of whom 826 were randomized to placebo ($n = 275$), 10,000 JAU ($n = 274$), or 20,000 JAU ($n = 277$). The number of withdrawals during period 2 was slightly higher in the active drug groups than in the placebo group primarily due to adverse events, whereas there was no difference between the 3 groups in the number of withdrawals during period 3.

There were no significant differences in demographic and asthma characteristics among the groups at baseline (Table 1). The mean age was 38.2 years, and the mean duration of asthma was 17.4 years. Approximately half the subjects had polysensitization to 3 or more allergens other than HDM, whereas 13.5% of all subjects were HDM-monosensitized. Overall 80% of subjects also had allergic rhinitis. At randomization, the mean FEV₁ was 88.5% of predicted value. Three-quarters of the subjects used 400 µg of fluticasone propionate per day at randomization, whereas the vast majority of the remainder used 200 µg daily.

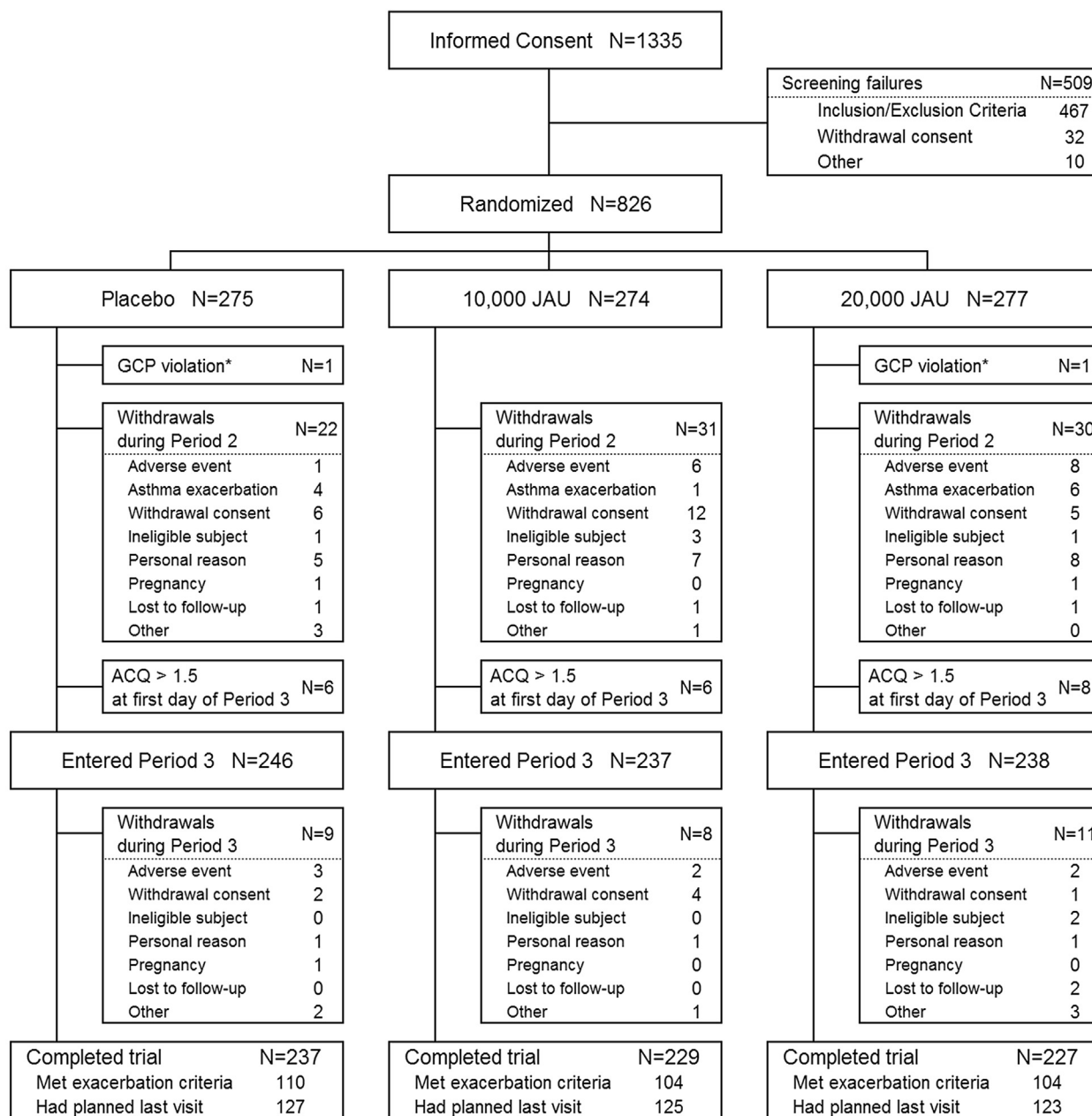


FIGURE 2. Subjects' disposition. *Duplicate enrollment: 1 subject was enrolled at 2 different sites, and assigned to the placebo and 20,000 JAU groups.

No significant differences in demographic characteristics at baseline were noted between the subjects who did or did not use SABA during the baseline period (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org). Baseline ICS use was similar between the subjects who did and did not require SABA. The mean total asthma symptom score during the baseline period was higher in those who required SABA (2.09) than in those who did not (1.35) (Table II).

Efficacy

No statistically significant differences were noted between the placebo group and both active groups for the primary and key secondary end points (Table III; Figure 3, A and B). Similarly, no

statistically significant differences were observed during period 3 in the other efficacy end points, such as moderate or severe asthma exacerbations, each asthma symptom score, lung function, or quality of life (Asthma Health Questionnaire-JAPAN) (data not shown).

The immunologic responses as indicated by *D fariniae*-specific IgE and IgG₄ levels in both active groups were higher than those in the placebo group at all measurement points (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Therefore, further post hoc subgroup analyses were performed to better understand the lack of efficacy in this trial. The results of post hoc subgroup analysis of the hazard ratio for asthma

TABLE I. Demographic and baseline asthma characteristics

Treatment group	Placebo (N = 274)	10,000 JAU (N = 274)	20,000 JAU (N = 276)	Active all (N = 550)	Overall (N = 824)
Demographic characteristic					
Sex, n (%)					
Male	149 (54.4)	142 (51.8)	130 (47.1)	272 (49.5)	421 (51.1)
Female	125 (45.6)	132 (48.2)	146 (52.9)	278 (50.5)	403 (48.9)
Age (y)					
Mean $\pm$ SD	37.9 $\pm$ 9.4	38.4 $\pm$ 10.6	38.3 $\pm$ 9.9	38.3 $\pm$ 10.3	38.2 $\pm$ 10.0
Median (range)	38.0 (18 to 64)	38.0 (18 to 64)	38.0 (19 to 63)	38.0 (18 to 64)	38.0 (18 to 64)
Years with HDM asthma					
Mean $\pm$ SD	17.5 $\pm$ 13.5	17.3 $\pm$ 13.0	17.4 $\pm$ 13.3	17.4 $\pm$ 13.1	17.4 $\pm$ 13.3
Median (range)	16.0 (0 to 52)	16.0 (0 to 57)	17.0 (0 to 58)	16.0 (0 to 58)	16.0 (0 to 58)
Age at onset (y)					
Mean $\pm$ SD	19.5 $\pm$ 15.2	20.1 $\pm$ 15.4	19.9 $\pm$ 15.5	20.0 $\pm$ 15.4	19.8 $\pm$ 15.4
Median (range)	19.0 (0 to 59)	20.0 (0 to 60)	21.0 (0 to 55)	21.0 (0 to 60)	20.0 (0 to 60)
Sensitization status, n (%)					
Monosensitized	47 (17.2)	33 (12.0)	31 (11.2)	64 (11.6)	111 (13.5)
1 other than HDM	41 (15.0)	38 (13.9)	46 (16.7)	84 (15.3)	125 (15.2)
2 other than HDM	43 (15.7)	50 (18.2)	44 (15.9)	94 (17.1)	137 (16.6)
≥ 3 other than HDM	143 (52.2)	153 (55.8)	155 (56.2)	308 (56.0)	451 (54.7)
Allergic rhinitis, n (%)					
None	60 (21.9)	55 (20.1)	52 (18.8)	107 (19.5)	167 (20.3)
Only seasonal	96 (35.0)	84 (30.7)	99 (35.9)	183 (33.3)	279 (33.9)
Only perennial	54 (19.7)	62 (22.6)	56 (20.3)	118 (21.5)	172 (20.9)
Seasonal + perennial	64 (23.4)	73 (26.6)	69 (25.0)	142 (25.8)	206 (25.0)
Specific IgE (kU/L), <i>D. farinae</i> , n (%)					
<17.5	103 (37.6)	80 (29.2)	90 (32.6)	170 (30.9)	273 (33.1)
17.5 to <50	88 (32.1)	94 (34.3)	96 (34.8)	190 (34.5)	278 (33.7)
50 to <100	41 (15.0)	54 (19.7)	48 (17.4)	102 (18.5)	143 (17.4)
≥ 100	42 (15.3)	46 (16.8)	42 (15.2)	88 (16.0)	130 (15.8)
Asthma characteristics during the 14-d baseline period					
Total asthma symptom score*					
Mean $\pm$ SD	1.62 $\pm$ 1.45	1.81 $\pm$ 1.57	1.66 $\pm$ 1.48	1.74 $\pm$ 1.53	1.70 $\pm$ 1.50
Median (range)	1.23 (0.0 to 6.4)	1.39 (0.0 to 6.9)	1.32 (0.0 to 8.0)	1.36 (0.0 to 8.0)	1.29 (0.0 to 8.0)
No. of nocturnal awakening due to asthma symptoms per night					
Mean $\pm$ SD	0.10 $\pm$ 0.21	0.13 $\pm$ 0.27	0.16 $\pm$ 0.35	0.15 $\pm$ 0.31	0.13 $\pm$ 0.28
Median (range)	0.00 (0.0 to 2.0)	0.00 (0.0 to 1.6)	0.00 (0.0 to 3.7)	0.00 (0.0 to 3.7)	0.00 (0.0 to 3.7)
24-h SABA use, no. of puffs					
Mean $\pm$ SD	0.37 $\pm$ 0.75	0.48 $\pm$ 1.04	0.42 $\pm$ 0.75	0.45 $\pm$ 0.90	0.42 $\pm$ 0.86
Median (range)	0.00 (0.0 to 5.1)	0.00 (0.0 to 6.6)	0.00 (0.0 to 4.1)	0.00 (0.0 to 6.6)	0.00 (0.0 to 6.6)
Average morning PEF (L/min)					
Mean $\pm$ SD	423 $\pm$ 104	419 $\pm$ 103	404 $\pm$ 97	411 $\pm$ 100	415 $\pm$ 102
Median (range)	417 (149 to 670)	413 (186 to 639)	401 (168 to 730)	406 (168 to 730)	409 (149 to 730)
Average evening PEF (L/min)					
Mean $\pm$ SD	441 $\pm$ 106	435 $\pm$ 105	423 $\pm$ 96	429 $\pm$ 100	433 $\pm$ 102
Median (range)	432 (151 to 691)	427 (191 to 696)	420 (169 to 726)	424 (169 to 726)	425 (151 to 726)
Average diurnal variation in PEF (%)					
Mean $\pm$ SD	3.39 $\pm$ 8.25	3.46 $\pm$ 6.96	4.25 $\pm$ 7.83	3.86 $\pm$ 7.41	3.70 $\pm$ 7.70
Median (range)	2.00 (−59.0 to 45.8)	1.55 (−14.4 to 39.1)	1.88 (−32.4 to 34.0)	1.77 (−32.4 to 39.1)	1.84 (−59.0 to 45.8)

(continued)

TABLE 1. (Continued)

Treatment group	Placebo (N = 274)	10,000 JAU (N = 274)	20,000 JAU (N = 276)	Active all (N = 550)	Overall (N = 824)
Asthma characteristics at randomization					
FEV ₁ (L)					
Mean $\pm$ SD	2.96 $\pm$ 0.74	2.90 $\pm$ 0.76	2.81 $\pm$ 0.74	2.86 $\pm$ 0.75	2.89 $\pm$ 0.75
Median (range)	2.91 (1.3 to 5.3)	2.85 (1.3 to 5.7)	2.69 (1.3 to 5.1)	2.75 (1.3 to 5.7)	2.85 (1.3 to 5.7)
FEV ₁ , % of predicted value					
Mean $\pm$ SD	88.8 $\pm$ 14.7	89.1 $\pm$ 13.8	87.4 $\pm$ 14.3	88.3 $\pm$ 14.0	88.5 $\pm$ 14.2
Median (range)	86.9 (47 to 147)	88.2 (59 to 135)	85.6 (62 to 133)	87.4 (59 to 135)	87.3 (47 to 147)
ACQ score					
Mean $\pm$ SD	1.19 $\pm$ 0.17	1.20 $\pm$ 0.17	1.21 $\pm$ 0.17	1.20 $\pm$ 0.17	1.20 $\pm$ 0.17
Median (range)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)
ICS, μ g of fluticasone propionate per day, n (%)					
200	71 (25.9)	58 (21.2)	68 (24.6)	126 (22.9)	197 (23.9)
300	2 (0.7)	0 (0.0)	1 (0.4)	1 (0.2)	3 (0.4)
400	201 (73.4)	216 (78.8)	207 (75.0)	423 (76.9)	624 (75.7)

PEF, Peak expiratory flow.

*Total asthma symptom score (range, 0-12): sum of each asthma symptom score (wheezing, coughing, shortness of breath, and chest tightness) during the day on a 0-3 scale (0, no symptom; 1, mild; 2, moderate; 3, severe).

exacerbation during period 3 are shown in Figure 4. For those who used a SABA during the 14-day baseline period, there was a statistically significant difference favoring 20,000 JAU over placebo in the hazard ratio for asthma exacerbation during period 3. Among the 2 actively treated groups, subgroup analyses of other baseline parameters (total or individual asthma symptom scores, peak expiratory flow, FEV₁, ACQ score, daily ICS dose, sensitization status, or comorbidity of perennial rhinitis) did not demonstrate significant differences. Post hoc stratified analyses of the primary and key secondary end points indicated that, for all subjects on active treatment who used SABA during the baseline period, there was a statistically better result on the log-rank test for the primary end point ($P = .044$) and a lower hazard ratio for the key secondary end point ($P = .036$) (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). For that subgroup, the difference between the placebo and the active groups was in the proportion of subjects with an asthma exacerbation after discontinuing ICS completely (Figure 3, C). For the subgroup not using SABA during the baseline period, there were no significant differences among the 3 groups throughout the ICS reduction period (Figure 3, D).

No correlation was noted between the ACQ scores and the e-diary data in shortness of breath and wheeze ($r = 0.05$ and 0.29). Conversely, a correlation was noted between the ACQ scores and the e-diary data in nocturnal awakening and SABA use ($r = 0.58$ and 0.81) (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Safety

The proportion of subjects experiencing serious adverse events was similar among the 3 groups. No investigational medicinal product (IMP)-related serious adverse events were noted, except for 1 case of autoimmune hepatitis in the placebo group (Table IV). Overall, 766 (93.0%) subjects experienced an adverse event, with no marked differences between the placebo (88.7%),

10,000 JAU (93.8%), and 20,000 JAU (96.4%) groups. Most events were mild or moderate in severity (99%, overall).

The proportion of subjects with IMP-related adverse events was higher in the active groups (62.8% in the 10,000 JAU group and 67.0% in the 20,000 JAU group) than in the placebo group (26.3%). All IMP-related adverse events in the active groups were mild or moderate, and the only severe IMP-related event was in the placebo group. The most frequently occurring IMP-related adverse events were local allergic reaction including oral discomfort, oral pruritus, and mouth edema.

No investigator-assessed anaphylactic reactions were reported. The 3 groups did not differ in the asthma-related adverse events assessed by investigators during period 2 (placebo, 18.2%; 10,000 JAU, 16.8%; 20,000 JAU, 21.7%). Proportion of subjects discontinuing owing to adverse events was more frequent in the 20,000 JAU group (5.8%) than in the placebo group (2.9%) or the 10,000 JAU group (3.3%). Numbers of subjects with IMP-related adverse events leading to treatment interruption were similar among all 3 groups. The proportion of subjects who experienced adverse events in each subgroup was similar between the subjects who did and did not require SABA during the baseline period (see Tables E7 and E8 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This is the first randomized, double-blind, placebo-controlled phase II/III trial of the SQ HDM SLIT tablet in Japanese adults with HDM AA.

No statistically significant differences between the placebo and active treatment groups were found for the primary or secondary end points, including moderate or severe asthma exacerbations, individual asthma symptom scores (cough, wheezing, shortness of breath, chest tightness), lung function, and quality of life. Changes from baseline in HDM-specific IgE and IgG₄ levels were similar to those in the SQ HDM SLIT-tablet asthma trial in

TABLE II. Asthma treatment and symptom levels during the 14-d baseline period

Subgroup	No. of subjects	ICS dose during baseline (fluticasone propionate)			24-h SABA use (no. of puffs), mean $\pm$ SD	Total asthma symptom score*, mean $\pm$ SD
		200 μ g/d	>200 to 400 μ g/d	>400 μ g/d		
All subjects	824	24%	76%	0%	0.42 $\pm$ 0.86	1.70 $\pm$ 1.50
Without SABA	433	26%	74%	0%	0.00 $\pm$ 0.00	1.35 $\pm$ 1.45
With SABA	391	21%	79%	0%	0.89 $\pm$ 1.06	2.09 $\pm$ 1.46

*Total asthma symptom score (range, 0-12): sum of each asthma symptom score (wheezing, coughing, shortness of breath, and chest tightness) during the day on a 0-3 scale (0, no symptom; 1, mild; 2, moderate; 3, severe).

TABLE III. Analysis of the primary and key secondary end points

Primary end point: Time in days from randomization to first asthma exacerbation (FAS)

Treatment group	No. of subjects				Log-rank test, <i>P</i> value		Cox proportional hazards regression, HR (95% CI)	
	Randomized	Censored		Asthma exacerbation in period 3	vs placebo	vs 10,000 JAU	vs placebo	vs 10,000 JAU
		Period 2*	Period 3†					
Placebo	274	28	136	110	—	—	—	—
10,000 JAU	274	37	133	104	0.716	—	0.95 (0.73-1.24)	—
20,000 JAU	276	38	134	104	0.828	0.881	0.97 (0.74-1.27)	1.02 (0.78-1.34)
Active all	550	75	267	208	0.738	—	0.96 (0.76-1.21)	—

Key secondary end point: Time in days from the start of period 3 to first asthma exacerbation (FAS-MI)

Treatment group	No. of subjects				Cox proportional hazards regression			
	Randomized	Censored		Asthma exacerbation in period 3	vs placebo		vs 10,000 JAU	
		Period 2*	Period 3†		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Placebo	274	28	136	110	—	—	—	—
10,000 JAU	274	37	133	104	0.93 (0.71-1.21)	0.581	—	—
20,000 JAU	276	38	134	104	0.94 (0.72-1.23)	0.675	1.02 (0.78-1.34)	0.896
Active all	550	75	267	208	0.94 (0.75-1.18)	0.572	—	—

FAS-MI, Full analysis set-multiple imputation; HR, hazard ratio.

*Subjects who discontinued the trial during period 2 or whose ACQ score was more than 1.5 at the start of period 3.

†Subjects who discontinued the trial during period 3 or who had no asthma exacerbations during period 3.

Europe and the rhinitis trial in Japan, indicating that differences between our results and other trials were not considered to occur because of treatment noncompliance.

According to the GINA global strategy for asthma management and prevention,⁶ well-controlled asthma is defined as asthma symptoms or use of a SABA no more than twice in a week. The Japanese guidelines for adult asthma²⁵ are stricter, however, defining well-controlled asthma as no asthma symptoms or any use of a SABA for a week. Therefore, some individuals considered to have insufficiently controlled asthma by the Japanese guidelines would still have been classified as having well-controlled asthma in accordance with GINA criteria (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Additional factors that may explain different results in the 2 trials may have been differences in subject selection. In the European trial, 59% of subjects used less than or equal to 200 μ g of fluticasone propionate equivalent (≤ 400 μ g of budesonide), 32% used greater than 200 to 400 μ g, and 9% used greater than 400 μ g. During their 14-day baseline period, the frequency of daily SABA use was 1.32 ± 1.63 , and the mean total asthma symptom score was 2.64 ± 1.98 .¹⁸ Subjects in our trial were treated with higher ICS doses, resulting in asthma being well controlled without the requirement for a SABA and with a low total asthma symptom score. In spite of higher ICS doses, the ratio of asthma exacerbations during period

3 in our trial was higher than that in the European trial (see Table E9 in this article's Online Repository at www.jaci-inpractice.org). This may reflect the result that subjects with lower asthma symptom scores at baseline were more likely to meet the definition of asthma exacerbation during period 3 (data not shown). In the subgroup analyses of baseline data, SABA use in both active treatment groups was similar to that in the European trial during the baseline period, which directly and objectively indicates the degree of asthma control. The need for a SABA during the 14-day baseline period had a greater effect on the efficacy evaluation than did the daily ICS dose at randomization (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). For this reason, post hoc analysis was conducted for the subgroup of subjects requiring SABA use during the baseline period. Those in the active treatment groups who used SABA were at a significantly lower risk of experiencing a moderate or severe asthma exacerbation during ICS reduction ($P = .044$). In the post hoc analysis of subjects who progressed to period 3 in the FAS-observed cases, there was no difference in the rate of exacerbations among the 3 groups in subjects who did not use SABA at baseline. Presumably, the asthma symptoms in these subjects were sufficiently controlled by the daily ICS dose alone, so asthma exacerbations did not occur even when the ICS dose was reduced. Reportedly, the efficacy of ICSs may last for 3 months after the cessation of ICSs,²⁶ suggesting a carryover effect

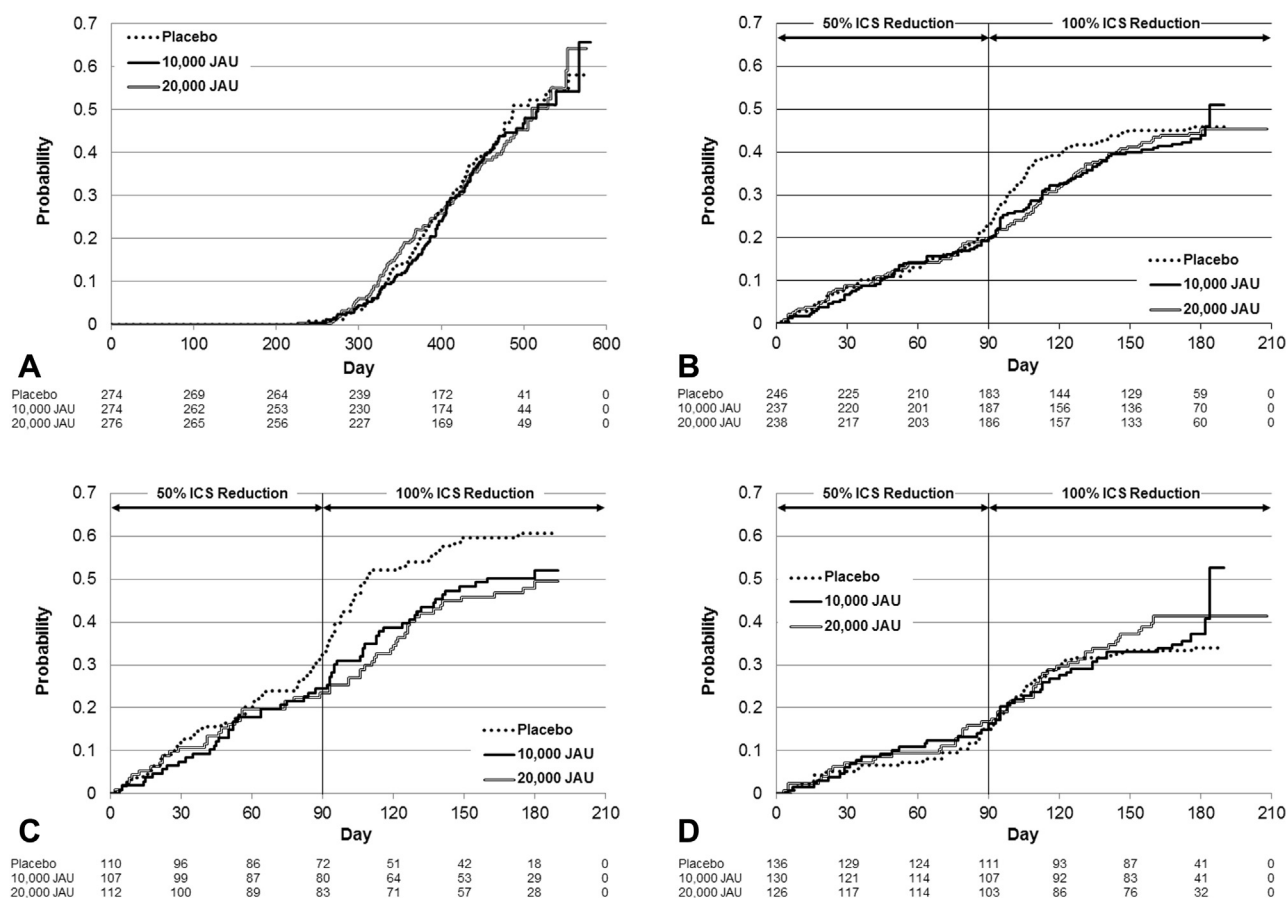


FIGURE 3. Probability of the first moderate or severe asthma exacerbation (**A**) from randomization (FAS), (**B**) from the start of ICS dose reduction, (**C**) from the start of ICS dose reduction among subjects who used SABA during the baseline period, and (**D**) from the start of ICS dose reduction in subjects who did not use SABA during the baseline period (FAS-observed cases).

of ICSs. Those factors may have influenced the efficacy evaluation that indicated no difference between the placebo and active groups even when ICSs were completely withdrawn. However, approximately 40% of randomized subjects had used SABA during the baseline period, and the subgroup analysis found that those in the 20,000 JAU group had fewer exacerbations than in the placebo group ($P = .04997$). Even so, there was no obvious difference between the placebo and active groups in the first 3 months of period 3 when the ICS dose was reduced by 50%, a finding slightly different from the results in the European trial that a difference between the active treatment group and the placebo group appeared shortly after the initial 50% ICS reduction period. The total asthma symptom score and the frequency of SABA use by subjects in the present trial were lower than those of subjects in the European trial even when considering only the subgroup of subjects who required SABA during the baseline period in our trial. For the subgroup of subjects who did not use SABA at baseline, all subjects had an ACQ score of 1.0 to 1.5 at randomization. However, 27% of those had no daytime asthma symptoms and nocturnal awakening for a week before randomization (data not shown), and were considered to be patients with likely well-controlled asthma on the basis of GINA criteria. There was no correlation between the ACQ scores, and the e-diary data subjectively reported items such as

shortness of breath and wheeze. Conversely, correlations were noted in nocturnal awakening and SABA use. Responses to those items were either yes or no. Thus, we found that the SQ HDM SLIT tablet was effective in reducing the frequency of exacerbations after ICS dose reduction and discontinuation in the subgroup of subjects using SABA at baseline. For these Japanese patients with HDM AA, the immunotherapy was effective in reducing exacerbations, just as it was in the European trial.¹⁸

Our findings regarding safety are similar to those in the European trial for HDM AA¹⁸ and the Japanese trials for HDM allergic rhinitis.^{14,15} No difference was noted in the severity and proportion of subjects with adverse events overall between the placebo and active groups. Most of the IMP-related adverse events reported in active groups were mild or moderate local allergic reactions. This trial therefore indicates a favorable safety profile of the SQ HDM SLIT tablet in Japanese patients with HDM AA.

CONCLUSIONS

In Japanese adults with HDM AA, the SQ HDM SLIT tablet was as safe as it was in the European asthma trial. The present trial possibly did not meet primary and secondary end points because of inclusion of subjects with well-controlled asthma. In the subgroup of subjects who required SABA

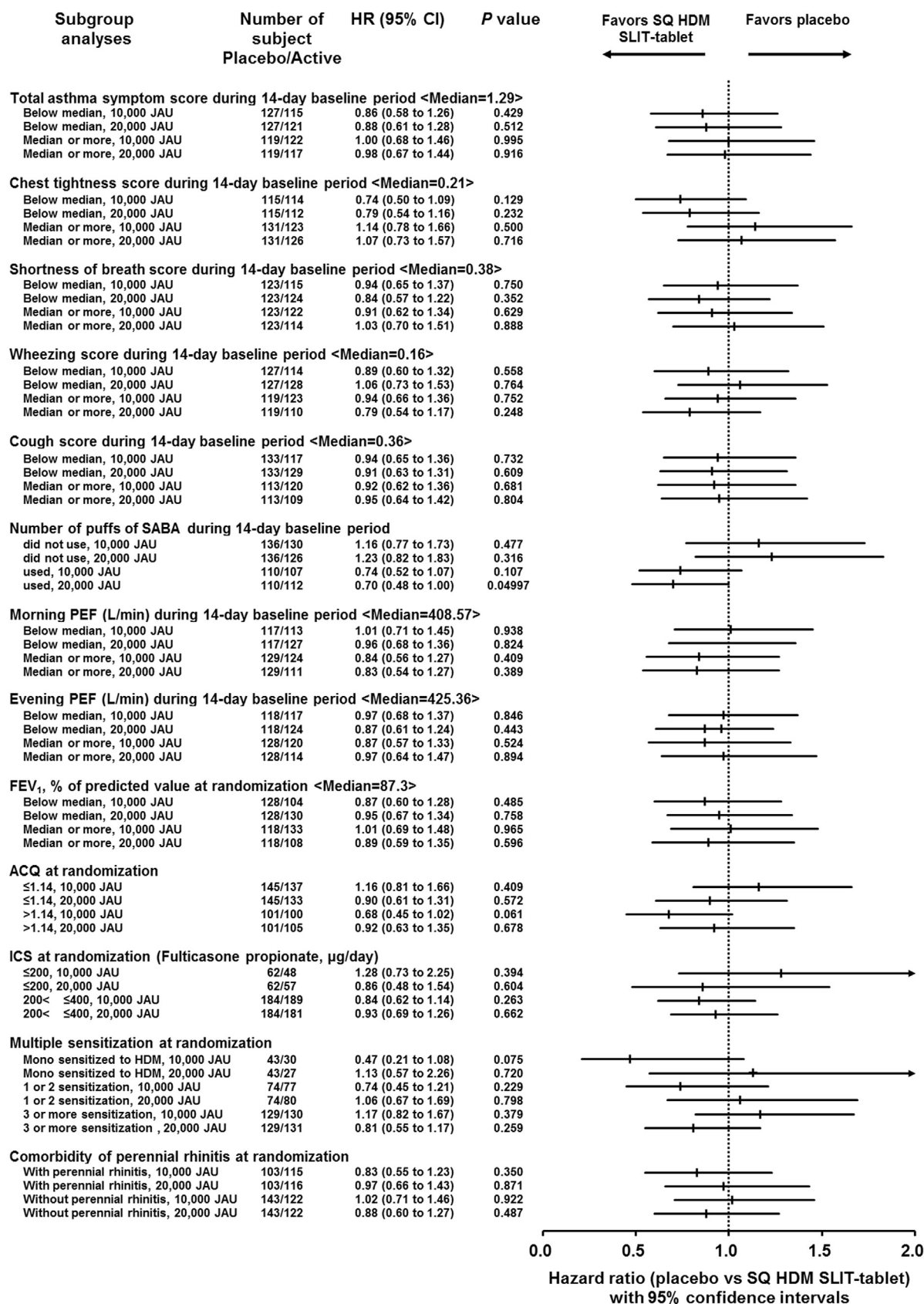


FIGURE 4. Forest plot of HRs for an asthma exacerbation during ICS dose reduction in the subgroup analyses (FAS-OC). FAS-OC, FAS-observed cases; HR, hazard ratio.

TABLE IV. Summary of AEs

Treatment group	Placebo (N = 274)		10,000 JAU (N = 274)		20,000 JAU (N = 276)	
	e	n (%)	e	n (%)	e	n (%)
SAE	13	11 (4.0)	7	7 (2.6)	13	10 (3.6)
IMP-related SAE	3	1 (0.4)	0	0	0	0
AE						
All	1091	243 (88.7)	1385	257 (93.8)	1495	266 (96.4)
Mild	964	168 (61.3)	1254	181 (66.1)	1334	175 (63.4)
Moderate	123	73 (26.6)	130	75 (27.4)	154	87 (31.5)
Severe	4	2 (0.7)	1	1 (0.4)	7	4 (1.4)
IMP-related AE						
All IMP-related AEs	138	72 (26.3)	371	172 (62.8)	413	185 (67.0)
Mild	126	63 (23.0)	358	162 (59.1)	395	171 (62.0)
Moderate	9	8 (2.9)	13	10 (3.6)	18	14 (5.1)
Severe	3	1 (0.4)	0	0	0	0
Significant AEs						
Anaphylactic reaction	0	0	0	0	0	0
Asthma during period 2*	77	50 (18.2)	92	46 (16.8)	109	60 (21.7)
AEs leading to discontinuation†	12	8 (2.9)	14	9 (3.3)	33	16 (5.8)
IMP-related AEs leading to interruption‡	13	8 (2.9)	9	7 (2.6)	11	5 (1.8)
Common IMP-related AEs§						
Oral discomfort	11	11 (4.0)	59	52 (19.0)	66	57 (20.7)
Oral pruritus	5	5 (1.8)	37	37 (13.5)	39	37 (13.4)
Edema mouth	3	3 (1.1)	34	31 (11.3)	46	40 (14.5)
Throat irritation	2	2 (0.7)	29	28 (10.2)	35	33 (12.0)
Oropharyngeal discomfort	11	11 (4.0)	23	22 (8.0)	34	28 (10.1)
Paresthesia oral	2	2 (0.7)	24	22 (8.0)	29	28 (10.1)
Ear pruritus	1	1 (0.4)	21	19 (6.9)	26	25 (9.1)
Lip swelling	0	0	8	7 (2.6)	9	8 (2.9)
Swollen tongue	0	0	5	5 (1.8)	10	9 (3.3)
Stomatitis	10	7 (2.6)	8	6 (2.2)	6	5 (1.8)
Abdominal discomfort	0	0	8	6 (2.2)	5	5 (1.8)
Lip pruritus	0	0	5	5 (1.8)	6	6 (2.2)

AE, Adverse event; e, number of events; n, number of subjects with event; MedDRA/J, Medical Dictionary for Regulatory Activities/J; SAE, serious adverse event.

*Including subjects with SAEs (1 subject in the placebo group and 1 in the 20,000 JAU group).

†Including subjects with SAEs (1 subject in the placebo group, 1 in the 10,000 JAU group, and 3 in the 20,000 JAU group); subjects with asthma during period 2 (4 subjects in the placebo group, 1 in the 10,000 JAU group, and 6 in the 20,000 JAU group).

‡Including subjects with IMP-related asthma during period 2 (1 subject in the 10,000 JAU group).

§IMP-related AEs reported in at least 2% of subjects who received active treatment (MedDRA/J, preferred term).

during the baseline period, that is, subjects with not well-controlled asthma, the SQ HDM SLIT tablet was effective in reducing the frequency of asthma exacerbations, similar to the results in the European trial.

Acknowledgments

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ONLINE REPOSITORY

METHODS

Trial population

Main selection criteria included the following:

- Age 18 to 64 years and a clinical history consistent with asthma symptoms treated with ICS administration, including combination preparations for at least 6 months, with a daily dose of ICS at randomization between 200 and 400 µg of fluticasone propionate.
- A mean score of 1.0 or more on the ACQ at the start of the baseline period (or a mean score of ≥ 0.85 if long-acting β_2 agonists were used during the 7 days before the first day of the screening period), with a mean score of 1.0 to 1.5 on the ACQ at randomization.
- Positive specific IgE against *D pteronyssinus* and/or *D farinae* (defined as specific IgE ≥ 3.5 kU/L) at the start of the baseline period.
- Positive skin scratch or prick test result for *D pteronyssinus* and/or *D farinae* at the start of the screening period.
- Confirmed reversible airway obstruction before the screening period or checked during the screening period, with at least 1 of the following criteria being met.
 1. Improvement of greater than or equal to 12% and 200 mL in absolute FEV₁ after administration of a SABA.
 2. Greater than 20% improvement in peak expiratory flow (PEF) after administration of a SABA.
 3. Greater than 20% diurnal variability in PEF after administration of a SABA.
- FEV₁ greater than 70% of predicted value at the start of the screening period.
- No history of persistent allergic asthma or rhinitis caused by an allergen to which the subject was regularly exposed and sensitized (except HDM).
- No history of immunotherapy with an HDM allergen for more than 1 month within the previous 5 years, and not on immunotherapy other than HDM at the start of the screening period.
- No hospitalizations due to asthma exacerbation within 3 months before the start of the screening period.
- No current clinically relevant symptoms of or treatment for infections such as upper respiratory tract infection, acute sinusitis, or acute otitis media, and no abnormalities in the oral cavity such as ulcerative stomatitis or inflammation at randomization.
- No systemic diseases affecting the immune system (eg, autoimmune diseases, immune complex diseases, and immunodeficiency diseases), and no respiratory diseases affecting the evaluation of efficacy and safety (eg, chronic obstructive pulmonary disease).

Assessment

The criteria for moderate and severe asthma exacerbation used in the present trial are presented in [Table E1](#).

Baseline values were defined as the mean values for each individual subject during the last 14 days of the screening period. Subjects meeting 1 or more of the criteria listed above were considered to have an asthma exacerbation. Criteria (a), (b), PEF

for (c), and (e) were assessed by entries in the e-diary. Investigators recorded the remaining criteria, including FEV₁ for (c), (d), and (f).

Sample size

Sample size calculation was based on the European trial of the SQ HDM SLIT tablet.^{E3} The trial provided the assumption that approximately 65% of subjects in the placebo group would experience an asthma exacerbation during period 3, with 13% of absolute difference and 0.70 hazard ratio (HR) between 10,000 JAU and placebo groups and that of 16% and 0.64 between 20,000 JAU and placebo groups. A reduction in the hazard rate for time to first asthma exacerbation of approximately 30%, corresponding to an HR of 0.70, was considered clinically relevant. In a simulation with SAS software using the above-mentioned hypothesis, treatment groups with 300 subjects each had a power of approximately 82% to reject the hypothesis that there are no differences among 3 groups between 10,000 JAU and placebo groups, and between 20,000 JAU and placebo groups, with a significance level of 5%. This assumed an estimated 10% and 4% discontinuation rate during periods 2 and 3, respectively. This sample size therefore yielded an approximately 82% power to detect a difference between both active groups combined and the placebo group. Further power calculations to detect a difference between the placebo group and 10,000 JAU or 20,000 JAU group are presented in [Table E2](#).

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 end point was the time from randomization to the first moderate or severe asthma exacerbation during period 3 with the population of FAS including all randomized subjects. The primary efficacy analysis was performed with the log-rank test. Multiplicity was controlled by a closed testing procedure that performs sequential testing starting from a high dose. The first hypothesis to be tested was that the placebo and 20,000 JAU groups were equal. Only if the test indicated a significant difference, a test to confirm the relationship between placebo and 10,000 JAU groups was performed. The key secondary end point was the time from the first day of period 3 to first moderate or severe asthma exacerbation during period 3 based on the FAS with multiple imputations of missing data. Thus, all subjects who withdraw during period 2 would be included as samples from the placebo distribution of time to first asthma exacerbation during period 3. The analysis was performed with a Cox proportional hazards regression model analysis adopting the treatment group as fixed effect. Multiplicity was controlled by the same procedure as the primary analysis. To investigate detailed factors that affected the efficacy evaluation, subgroup analyses were performed. Data during the baseline period (total and 4 asthma symptom scores, number of puffs of SABA for 24 hours, and morning and evening PEF) and data at randomization (the percentage of predicted value of FEV₁, ACQ score, ICS dose, and sensitization status) constituted the subjects' background data. Covariates were stratified in binary groups. Lung functions, that is, morning and evening PEF and FEV₁, total asthma symptom score, and 4 symptoms, were stratified by the median of each score. The ACQ score was separated between 8 and 9,

SABA use was classified as did or did not use, and the ICS dose was either low (≤ 200 $\mu\text{g}/\text{d}$) or high (>200 to 400 $\mu\text{g}/\text{d}$). Sensitization status was appropriately classified. For subgroup analyses of all above-mentioned background data, the population of FAS-observed cases (FAS-OC) that included subjects who entered period 3 was used. The subgroup analyses were performed with a Cox proportional hazards regression model analysis adopting the treatment group as fixed effect.

RESULTS

Population

Tables E3 and E4 present the stratified demographic and asthma characteristics divided by whether subjects did or did not use SABA in the FAS-OC. There was no difference in demographic data between these 2 groups, whereas the asthma control of those who used SABA was worse than that of those who did not. Those who used SABA had higher asthma symptom scores and ACQ scores and worse lung function compared with those who did not use SABA. Even those with poorer lung function, however, had well-controlled asthma.

Stratified analyses of primary and secondary end points

Post hoc analyses were performed on the primary (FAS) and secondary (FAS-OC) end points (Table E5). The randomized subjects were stratified by whether or not they used SABA during the baseline period.

Among those who used SABA, a statistically significant difference was noted for the primary end point in both active groups combined compared with the placebo (log-rank test, $P = .044$). In the 20,000 JAU group, the HR of 0.71 by Cox proportional hazards regression almost satisfied predefined clinical relevance of Virchow et al,^{E4} even though the SABA use group included only 40% of the randomized subjects. The post hoc analysis of the secondary end point for the 20,000 JAU group was similar to that for the primary end point (HR, 0.70; $P = .04997$). For both active treatment groups combined, the HR was 0.72 ($P = .036$). In contrast, among subjects who did not use SABA during the baseline period, there were no differences between the active treatment groups and the placebo group for either the primary or the secondary end point.

Correlation between ACQ and e-diary

Comparing data from the questionnaire completed at the site visit and daily e-diary data entry showed that objectively evaluated variables such as SABA use and nocturnal awakenings were correlated ($r = 0.81$ and 0.58), whereas subjectively evaluated variables such as shortness of breath and wheeze ($r = 0.05$ and 0.29) were not correlated (Table E6).

Stratified safety profile

No marked differences between those with and without SABA use were found in the stratified safety analysis except for serious adverse events and asthma during period 2. Those who used SABA had a higher incidence of serious adverse events, but the incidence of IMP-related serious adverse events was the same between the 2 groups. Analysis of asthma exacerbations during period 2 indicated that the degree of asthma control during the baseline period affected the incidence of exacerbations (Tables E7 and E8).

Immunology

The present trial showed immunologic changes comparable with published data regardless of the differences in subpopulations.^{E4-E6} Both HDM-specific IgE and IgG₄ levels rapidly increased. However, later in the study period, HDM-specific IgE levels decreased, whereas HDM-specific IgG₄ levels slightly increased (Figure E1).

Comparison of asthma control

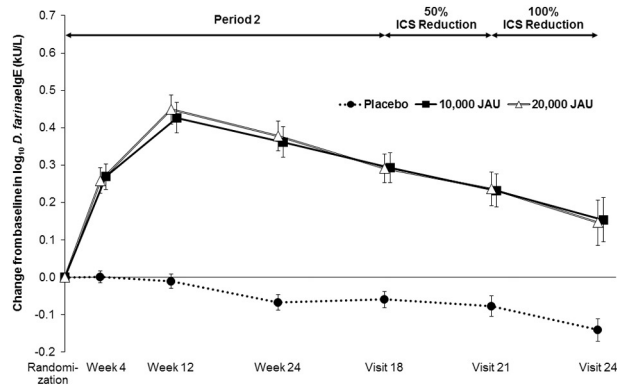
Figure E2 compares the criteria for well-controlled asthma according to the GINA global strategy for asthma management and prevention and Japanese guidelines for adult asthma. The former allow asthma symptoms or SABA use twice a week or less, whereas the latter includes only those patients who have no asthma symptoms and do not need to use SABA. These differences in the definition of subject backgrounds may have affected the results of the study.

Factors affecting asthma control

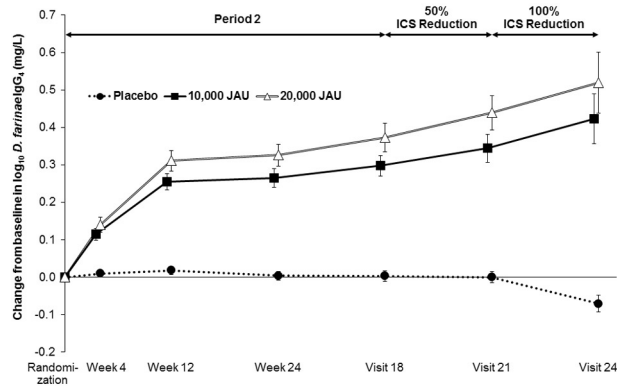
The subjects in the placebo group who progressed to period 3 (FAS-OC) were stratified in 4 groups by whether they used SABA during the baseline period and the ICS dose at randomization (Figure E3). The analysis indicated that SABA use rather than the ICS dose was useful in choosing the subjects for efficacy evaluation by the asthma exacerbation rate during the period of ICS reduction.

Comparison with European trial

Table E9 presents the comparison of asthma exacerbation(s) during period 3 between the present trial and the European trial. The number of discontinued subjects during period 2 in each treatment group was similar between the 2 trials. However, discontinued subjects during period 3 in the present trial were less than those in the European trial, and subjects with moderate or severe asthma exacerbation(s) during period 3 in the present trial were more than those in the European trial.



A



B

FIGURE E1. Means with 95% CIs of immunologic parameters, indicating changes from baseline levels of (A) *D. farinae* IgE and (B) *D. farinae* IgG₄ throughout the trial (ITT). Means and CIs were calculated using $\log_{10}$ -transformed data. *ITT*, Intention-to-treat; *kU/L*, kilo-units per liter.

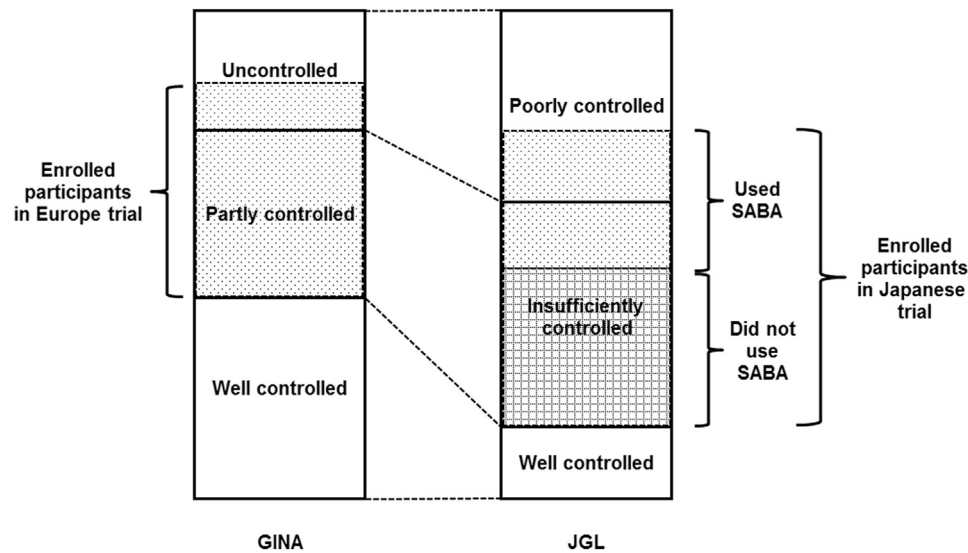


FIGURE E2. Daily asthma control level of enrolled subjects in compliance with guidelines used in the European and Japanese trials. *JGL*, Japanese guidelines for adults asthma.

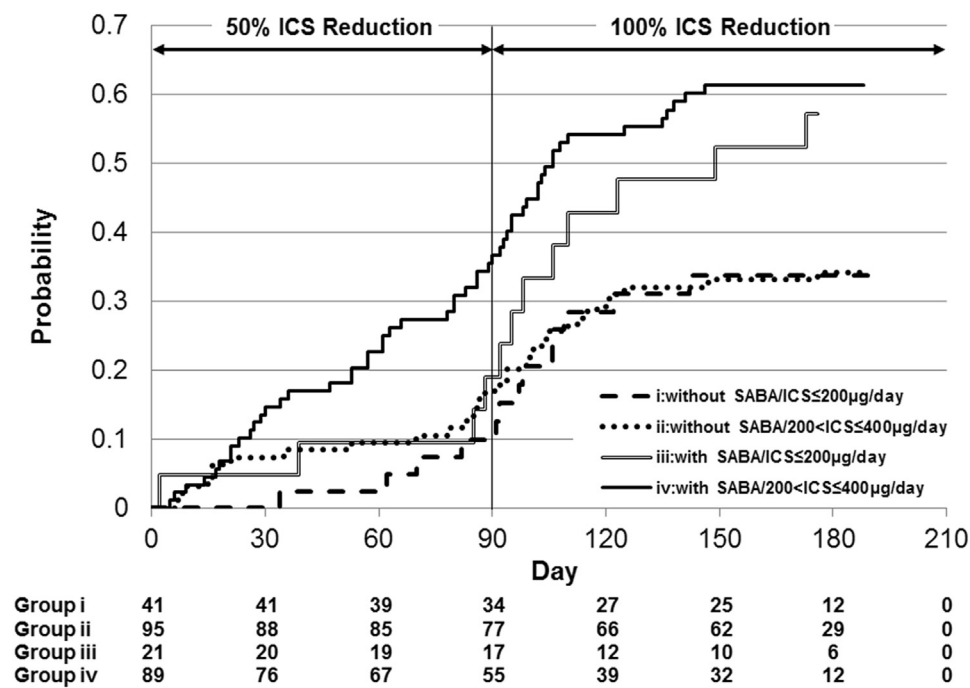


FIGURE E3. Subpopulation analysis in the placebo group of the probability of the first moderate or severe asthma exacerbation from the start of ICS reduction period (period 3) in those using SABA during the baseline period and ICS dose at randomization (FAS-OC).

TABLE E1. Criteria for moderate and severe asthma exacerbation***Moderate exacerbation**

- (a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of at least 0.75 points in daily symptom score from baseline value on at least 2 consecutive days
- (b) An increase from baseline in SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
- (c) A 20% or more decrease in morning or evening PEF from baseline on at least 2 consecutive days or a 20% or more decrease in FEV₁ from baseline
- (d) A visit to the emergency department or an unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids

Severe exacerbation

- (e) A requirement of systemic corticosteroids for the treatment of asthma symptoms
- (f) An emergency department visit due to asthma requiring systemic corticosteroids, or a hospitalization due to asthma

*Defined according to the American Thoracic Society and the European Respiratory Society recommendations.^{E1,E2}

TABLE E2. Power for statistical analysis

Hypotheses to be rejected	Power to reject (N = 300)
Placebo = 10,000 JAU = 20,000 JAU	95%
Placebo = 10,000 JAU = 20,000 JAU and Placebo = 20,000 JAU	94%
Placebo = 10,000 JAU = 20,000 JAU and Placebo = 10,000 JAU	83%
Placebo = 10,000 JAU = 20,000 JAU and Placebo = 20,000 JAU and Placebo = 10,000 JAU	82%

TABLE E3. Comparison of demographic and asthma characteristics in subjects who did use SABA during the 14-d baseline period (FAS-OC)

Treatment group	Placebo (N = 110)	10,000 JAU (N = 107)	20,000 JAU (N = 112)	Active all (N = 219)	Overall (N = 329)
Demographic characteristic					
Sex, n (%)					
Male	63 (57.3)	55 (51.4)	60 (53.6)	115 (52.5)	178 (54.1)
Female	47 (42.7)	52 (48.6)	52 (46.4)	104 (47.5)	151 (45.9)
Age (y)					
Mean $\pm$ SD	38.8 $\pm$ 8.7	39.0 $\pm$ 10.0	39.1 $\pm$ 9.1	39.1 $\pm$ 9.5	39.0 $\pm$ 9.2
Median (range)	39.0 (20 to 64)	39.0 (18 to 62)	38.5 (19 to 59)	39.0 (18 to 62)	39.0 (18 to 64)
Years with HDM asthma					
Mean $\pm$ SD	19.0 $\pm$ 14.1	17.4 $\pm$ 12.7	20.5 $\pm$ 13.6	19.0 $\pm$ 13.2	19.0 $\pm$ 13.5
Median (range)	18.0 (0 to 48)	17.0 (0 to 46)	21.5 (0 to 49)	19.0 (0 to 49)	19.0 (0 to 49)
Age at onset (y)					
Mean $\pm$ SD	18.8 $\pm$ 15.0	20.7 $\pm$ 15.1	17.6 $\pm$ 15.2	19.1 $\pm$ 15.2	19.0 $\pm$ 15.1
Median (range)	19.5 (0 to 54)	22.0 (0 to 51)	14.0 (0 to 54)	20.0 (0 to 54)	20.0 (0 to 54)
Sensitization status, n (%)					
Monosensitized	24 (21.8)	12 (11.2)	15 (13.4)	27 (12.3)	51 (15.5)
1 other than HDM	13 (11.8)	14 (13.1)	21 (18.8)	35 (16.0)	48 (14.6)
2 other than HDM	13 (11.8)	16 (15.0)	17 (15.2)	33 (15.1)	46 (14.0)
≥ 3 other than HDM	60 (54.5)	65 (60.7)	59 (52.7)	124 (56.6)	184 (55.9)
Allergic rhinitis, n (%)					
None	33 (30.0)	20 (18.7)	27 (24.1)	47 (21.5)	80 (24.3)
Only seasonal	37 (33.6)	37 (34.6)	33 (29.5)	70 (32.0)	107 (32.5)
Only perennial	23 (20.9)	25 (23.4)	18 (16.1)	43 (19.6)	66 (20.1)
Seasonal + perennial	17 (15.5)	25 (23.4)	34 (30.4)	59 (26.9)	76 (23.1)
Specific IgE (kU/L), <i>D. farinae</i> , n (%)					
<17.5	37 (33.6)	26 (24.3)	38 (33.9)	64 (29.2)	101 (30.7)
17.5 to <50	37 (33.6)	33 (30.8)	40 (35.7)	73 (33.3)	110 (33.4)
50 to <100	21 (19.1)	28 (26.2)	13 (11.6)	41 (18.7)	62 (18.8)
≥ 100	15 (13.6)	20 (18.7)	21 (18.8)	41 (18.7)	56 (17.0)
Asthma characteristics during the 14-d baseline period					
Total asthma symptom score*					
Mean $\pm$ SD	2.00 $\pm$ 1.42	2.13 $\pm$ 1.53	2.09 $\pm$ 1.36	2.11 $\pm$ 1.44	2.08 $\pm$ 1.43
Median (range)	1.57 (0.0 to 6.4)	1.79 (0.0 to 6.9)	1.79 (0.0 to 5.9)	1.79 (0.0 to 6.9)	1.71 (0.0 to 6.9)
No. of nocturnal awakening due to asthma symptoms per night					
Mean $\pm$ SD	0.16 $\pm$ 0.28	0.19 $\pm$ 0.29	0.25 $\pm$ 0.34	0.23 $\pm$ 0.32	0.20 $\pm$ 0.30
Median (range)	0.07 (0.0 to 2.0)	0.07 (0.0 to 1.3)	0.14 (0.0 to 2.0)	0.07 (0.0 to 2.0)	0.07 (0.0 to 2.0)
24-h SABA use, no. of puffs					
Mean $\pm$ SD	0.77 $\pm$ 0.91	0.93 $\pm$ 1.18	0.88 $\pm$ 0.93	0.90 $\pm$ 1.06	0.86 $\pm$ 1.01
Median (range)	0.43 (0.1 to 5.1)	0.36 (0.1 to 4.9)	0.55 (0.1 to 4.1)	0.43 (0.1 to 4.9)	0.43 (0.1 to 5.1)
Average morning PEF (L/min)					
Mean $\pm$ SD	406 $\pm$ 101	396 $\pm$ 93	384 $\pm$ 94	390 $\pm$ 93	395 $\pm$ 96
Median (range)	400 (204 to 619)	399 (192 to 639)	375 (176 to 646)	391 (176 to 646)	396 (176 to 646)
Average evening PEF (L/min)					
Mean $\pm$ SD	428 $\pm$ 102	412 $\pm$ 97	407 $\pm$ 93	409 $\pm$ 95	416 $\pm$ 98
Median (range)	423 (221 to 618)	414 (191 to 656)	404 (227 to 674)	411 (191 to 674)	413 (191 to 674)
Average diurnal variation in PEF (%)					
Mean $\pm$ SD	4.40 $\pm$ 8.32	3.15 $\pm$ 6.42	5.34 $\pm$ 9.16	4.27 $\pm$ 7.99	4.31 $\pm$ 8.09
Median (range)	2.16 (−12.5 to 45.8)	1.79 (−14.4 to 22.8)	2.24 (−32.4 to 34.0)	1.98 (−32.4 to 34.0)	2.01 (−32.4 to 45.8)
Asthma characteristics at randomization					
FEV ₁ (L)					
Mean $\pm$ SD	2.92 $\pm$ 0.75	2.85 $\pm$ 0.77	2.78 $\pm$ 0.74	2.81 $\pm$ 0.76	2.85 $\pm$ 0.75
Median (range)	2.91 (1.3 to 4.7)	2.74 (1.3 to 5.7)	2.66 (1.5 to 4.9)	2.71 (1.3 to 5.7)	2.75 (1.3 to 5.7)
FEV ₁ , % of predicted value					
Mean $\pm$ SD	87.1 $\pm$ 14.2	87.4 $\pm$ 14.4	84.4 $\pm$ 13.6	85.9 $\pm$ 14.1	86.3 $\pm$ 14.1

(continued)

TABLE E3. (Continued)

Treatment group	Placebo (N = 110)	10,000 JAU (N = 107)	20,000 JAU (N = 112)	Active all (N = 219)	Overall (N = 329)
Median (range)	86.2 (47 to 126)	86.8 (59 to 135)	83.4 (62 to 130)	84.0 (59 to 135)	85.2 (47 to 135)
ACQ score					
Mean $\pm$ SD	1.26 $\pm$ 0.16	1.25 $\pm$ 0.17	1.28 $\pm$ 0.16	1.26 $\pm$ 0.17	1.26 $\pm$ 0.16
Median (range)	1.29 (1.0 to 1.4)	1.29 (1.0 to 1.4)	1.29 (1.0 to 1.4)	1.29 (1.0 to 1.4)	1.29 (1.0 to 1.4)
ICS (μ g of fluticasone propionate per day), n (%)					
200	21 (19.1)	25 (23.4)	19 (17.0)	44 (20.1)	65 (19.8)
300	1 (0.9)	0 (0.0)	1 (0.9)	1 (0.5)	2 (0.6)
400	88 (80.0)	82 (76.6)	92 (82.1)	174 (79.5)	262 (79.6)

kU/L, Kilo-units per liter.

*Total asthma symptom score (range, 0-12): sum of each asthma symptom score (wheezing, coughing, shortness of breath, and chest tightness) during the day on a 0-3 scale (0, no symptom; 1, mild; 2, moderate; 3, severe).

TABLE E4. Comparison of demographic and asthma characteristics in subjects who did not use SABA during the 14-d baseline period (FAS-OC)

Treatment group	Placebo (N = 136)	10,000 JAU (N = 130)	20,000 JAU (N = 126)	Active all (N = 256)	Overall (N = 392)
Demographic characteristic					
Sex, n (%)					
Male	68 (50.0)	70 (53.8)	57 (45.2)	127 (49.6)	195 (49.7)
Female	68 (50.0)	60 (46.2)	69 (54.8)	129 (50.4)	197 (50.3)
Age (y)					
Mean $\pm$ SD	38.0 $\pm$ 9.8	38.8 $\pm$ 10.9	38.1 $\pm$ 9.9	38.4 $\pm$ 10.4	38.3 $\pm$ 10.2
Median (range)	38.5 (18 to 64)	39.0 (18 to 63)	37.5 (19 to 63)	38.0 (18 to 63)	38.0 (18 to 64)
Years with HDM asthma					
Mean $\pm$ SD	16.6 $\pm$ 13.3	16.2 $\pm$ 13.3	14.6 $\pm$ 12.8	15.4 $\pm$ 13.1	15.8 $\pm$ 13.1
Median (range)	15.0 (0 to 52)	14.5 (0 to 57)	12.0 (0 to 58)	14.0 (0 to 58)	14.0 (0 to 58)
Age at onset (y)					
Mean $\pm$ SD	20.4 $\pm$ 15.6	21.5 $\pm$ 15.8	22.5 $\pm$ 15.4	22.0 $\pm$ 15.6	21.5 $\pm$ 15.6
Median (range)	20.0 (0 to 57)	20.5 (0 to 60)	25.5 (0 to 53)	23.0 (0 to 60)	22.0 (0 to 60)
Sensitization status, n (%)					
Monosensitized	19 (14.0)	18 (13.8)	12 (9.5)	30 (11.7)	49 (12.5)
1 other than HDM	21 (15.4)	20 (15.4)	21 (16.7)	41 (16.0)	62 (15.8)
2 other than HDM	27 (19.9)	27 (20.8)	21 (16.7)	48 (18.8)	75 (19.1)
≥ 3 other than HDM	69 (50.7)	65 (50.0)	72 (57.1)	137 (53.5)	206 (52.6)
Allergic rhinitis, n (%)					
None	22 (16.2)	27 (20.8)	18 (14.3)	45 (17.6)	67 (17.1)
Only seasonal	51 (37.5)	38 (29.2)	44 (34.9)	82 (32.0)	133 (33.9)
Only perennial	22 (16.2)	25 (19.2)	29 (23.0)	54 (21.1)	76 (19.4)
Seasonal + perennial	41 (30.1)	40 (30.8)	35 (27.8)	75 (29.3)	116 (29.6)
Specific IgE (kU/L), <i>D. farinae</i> , n (%)					
<17.5	60 (44.1)	50 (38.5)	41 (32.5)	91 (35.5)	151 (38.5)
17.5 to <50	42 (30.9)	46 (35.4)	42 (33.3)	88 (34.4)	130 (33.2)
50 to <100	13 (9.6)	18 (13.8)	26 (20.6)	44 (17.2)	57 (14.5)
≥ 100	21 (15.4)	16 (12.3)	17 (13.5)	33 (12.9)	54 (13.8)
Asthma characteristics during the 14-d baseline period					
Total asthma symptom score*					
Mean $\pm$ SD	1.32 $\pm$ 1.38	1.51 $\pm$ 1.50	1.22 $\pm$ 1.43	1.37 $\pm$ 1.47	1.35 $\pm$ 1.44
Median (range)	0.86 (0.0 to 5.6)	0.93 (0.0 to 5.8)	0.68 (0.0 to 8.0)	0.89 (0.0 to 8.0)	0.86 (0.0 to 8.0)
No. of nocturnal awakening due to asthma symptoms per night					
Mean $\pm$ SD	0.05 $\pm$ 0.13	0.07 $\pm$ 0.22	0.09 $\pm$ 0.37	0.08 $\pm$ 0.31	0.07 $\pm$ 0.26
Median (range)	0.00 (0.0 to 0.9)	0.00 (0.0 to 1.6)	0.00 (0.0 to 3.7)	0.00 (0.0 to 3.7)	0.00 (0.0 to 3.7)
24-h SABA use, no. of puffs					
Mean $\pm$ SD	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00
Median (range)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)	0.00 (0.0 to 0.0)
Average morning PEF (L/min)					
Mean $\pm$ SD	434 $\pm$ 109	442 $\pm$ 105	425 $\pm$ 103	433 $\pm$ 104	434 $\pm$ 106
Median (range)	423 (149 to 670)	428 (201 to 637)	420 (168 to 730)	423 (168 to 730)	423 (149 to 730)
Average evening PEF (L/min)					
Mean $\pm$ SD	450 $\pm$ 111	457 $\pm$ 106	439 $\pm$ 102	448 $\pm$ 104	449 $\pm$ 106
Median (range)	440 (151 to 691)	440 (228 to 696)	435 (169 to 726)	437 (169 to 726)	438 (151 to 726)
Average diurnal variation in PEF (%)					
Mean $\pm$ SD	2.70 $\pm$ 8.69	3.21 $\pm$ 6.57	3.17 $\pm$ 6.46	3.19 $\pm$ 6.50	3.02 $\pm$ 7.33
Median (range)	2.02 (−59.0 to 37.0)	1.11 (−8.8 to 28.6)	1.42 (−13.6 to 27.9)	1.21 (−13.6 to 28.6)	1.40 (−59.0 to 37.0)
Asthma characteristics at randomization					
FEV ₁ (L)					
Mean $\pm$ SD	2.96 $\pm$ 0.76	2.95 $\pm$ 0.77	2.88 $\pm$ 0.75	2.91 $\pm$ 0.76	2.93 $\pm$ 0.76
Median (range)	2.90 (1.4 to 5.3)	2.89 (1.4 to 5.1)	2.78 (1.3 to 5.1)	2.87 (1.3 to 5.1)	2.88 (1.3 to 5.3)
FEV ₁ , % of predicted value					
Mean $\pm$ SD	90.7 $\pm$ 15.2	90.2 $\pm$ 13.0	89.9 $\pm$ 14.7	90.1 $\pm$ 13.9	90.3 $\pm$ 14.3

(continued)

TABLE E4. (Continued)

Treatment group	Placebo (N = 136)	10,000 JAU (N = 130)	20,000 JAU (N = 126)	Active all (N = 256)	Overall (N = 392)
Median (range)	87.5 (62 to 147)	89.1 (61 to 127)	88.9 (63 to 133)	89.0 (61 to 133)	88.7 (61 to 147)
ACQ score					
Mean $\pm$ SD	1.12 $\pm$ 0.15	1.14 $\pm$ 0.15	1.12 $\pm$ 0.14	1.13 $\pm$ 0.15	1.13 $\pm$ 0.15
Median (range)	1.00 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)	1.14 (1.0 to 1.4)
ICS (μ g of fluticasone propionate per day), n (%)					
200	41 (30.1)	23 (17.7)	38 (30.2)	61 (23.8)	102 (26.0)
300	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
400	94 (69.1)	107 (82.3)	88 (69.8)	195 (76.2)	289 (73.7)

kU/L, Kilo-units per liter.

*Total asthma symptom score (range, 0-12): sum of each asthma symptom score (wheezing, coughing, shortness of breath, and chest tightness) during the day on a 0-3 scale (0, no symptom; 1, mild; 2, moderate; 3, severe).

TABLE E5. Stratified analyses of primary and secondary end points**Time to first asthma exacerbation from randomization (FAS)**

Treatment group	No. of subjects				Log-rank, <i>P</i> value		Cox proportional hazards regression, HR (95% CI)	
	Randomized	Censored		Asthma exacerbation in period 3			vs placebo	vs 10,000 JAU
		Period 2	Period 3					
SABA used								
Placebo	125	15	45	65	—	—	—	—
10,000 JAU	132	25	53	54	0.116	—	0.75 (0.52-1.08)	—
20,000 JAU	134	22	59	53	0.061	0.763	0.71 (0.49-1.02)	0.94 (0.65-1.38)
Active all	266	47	112	107	0.044	—	0.73 (0.54-0.99)	—
SABA not used								
Placebo	149	13	91	45	—	—	—	—
10,000 JAU	142	12	80	50	0.380	—	1.20 (0.80-1.80)	—
20,000 JAU	142	16	75	51	0.171	0.631	1.32 (0.88-1.98)	1.10 (0.75-1.63)
Active all	284	28	155	101	0.199	—	1.26 (0.89-1.79)	—

Time to first asthma exacerbation from the start of period 3 (FAS-OC)

Treatment group	No. of subjects			Cox proportional hazards regression			
	Entered period 3	Censored	Asthma exacerbation	vs placebo		vs 10,000 JAU	
				HR (95% CI)	P value	HR (95% CI)	P Value
SABA used							
Placebo	110	45	65	—	—	—	—
10,000 JAU	107	53	54	0.74 (0.52-1.07)	0.107	—	—
20,000 JAU	112	59	53	0.70 (0.48-1.00)	0.04997	0.94 (0.64-1.37)	0.733
Active all	219	112	107	0.72 (0.53-0.98)	0.036	—	—
SABA not used							
Placebo	136	91	45	—	—	—	—
10,000 JAU	130	80	50	1.16 (0.77-1.73)	0.477	—	—
20,000 JAU	126	75	51	1.23 (0.82-1.83)	0.316	1.06 (0.72-1.57)	0.767
Active all	256	155	101	1.19 (0.84-1.69)	0.327	—	—

Means during 14-d baseline period by e-diary								
How much shortness of breath	0	>0 to 0.5	>0.5 to 1	>1 to 1.5	>1.5 to 2	>2 to 2.5	> 2.5 to 3	R
ACQ at randomization								
0 None	5	14	6	0	0	0	0	0.05
1 A very little	84	131	115	35	6	0	0	
2 A little	69	164	123	43	6	0	0	
3 A moderate amount	6	8	5	2	1	0	0	
4 Quite a lot	0	0	0	1	0	0	0	
5 A great deal	0	0	0	0	0	0	0	
6 A very great deal	0	0	0	0	0	0	0	
Means during 14-d baseline period by e-diary								
How much time spent wheezing	0	>0 to 0.5	>0.5 to 1	>1 to 1.5	>1.5 to 2	>2 to 2.5	>2.5 to 3	R
ACQ at randomization								
0 Never	51	23	6	0	0	0	0	0.29
1 Hardly any of the time	176	148	90	19	3	0	0	
2 A little of the time	59	109	91	20	1	0	0	
3 A moderate amount of the time	3	11	7	4	0	0	0	
4 A lot of the time	0	0	2	0	0	0	0	
5 Most of the time	0	0	1	0	0	0	0	
6 All the time	0	0	0	0	0	0	0	
Means during 14-d baseline period by e-diary								
How often awaking at night	0	>0 to 1/14	>1/14 to 2/14	>2/14 to 4/14	>4/14 to 7/14	>7/14 to 1	>1	R
ACQ at randomization								
0 Never	275	20	15	8	0	0	0	0.58
1 Hardly ever	202	51	35	28	28	14	2	
2 A few times	15	9	12	35	18	28	10	
3 Several times	0	0	2	3	7	4	1	
4 Many times	0	0	0	0	0	2	0	
5 A great many times	0	0	0	0	0	0	0	
6 Unable to sleep because of asthma	0	0	0	0	0	0	0	
Means during 14-d baseline period by e-diary								
How many puffs/inhalations of SABA most days	0	1-2	3-4	5-8	9-12	13-16	>16	R
ACQ at randomization								
0 None	420	73	1	0	0	0	0	0.81
1 1-2	13	263	20	1	0	0	0	
2 3-4	0	7	16	2	0	0	0	
3 5-8	0	1	1	6	0	0	0	
4 9-12	0	0	0	0	0	0	0	
5 13-16	0	0	0	0	0	0	0	
6 More than 16	0	0	0	0	0	0	0	

TABLE E7. Safety profile in subjects who did use SABA due to asthma symptoms during the 14-d baseline period

Treatment group	Placebo (N = 125)		10,000 JAU (N = 132)		20,000 JAU (N = 134)	
	e	n (%)	e	n (%)	e	n (%)
SAE	10	8 (6.4)	6	6 (4.5)	9	6 (4.5)
IMP-related SAE	3	1 (0.8)	0	0	0	0
AE						
All	451	109 (87.2)	674	121 (91.7)	779	128 (95.5)
Mild	391	77 (61.6)	610	80 (60.6)	674	75 (56.0)
Moderate	56	30 (24.0)	63	40 (30.3)	100	51 (38.1)
Severe	4	2 (1.6)	1	1 (0.8)	5	2 (1.5)
IMP-related AE						
All IMP-related AEs	52	34 (27.2)	180	79 (59.8)	210	85 (63.4)
Mild	46	30 (24.0)	174	75 (56.8)	200	78 (58.2)
Moderate	3	3 (2.4)	6	4 (3.0)	10	7 (5.2)
Severe	3	1 (0.8)	0	0	0	0
Significant AEs						
Anaphylactic reaction	0	0	0	0	0	0
Asthma during period 2*	41	27 (21.6)	54	26 (19.7)	73	38 (28.4)
AEs leading to discontinuation†	3	2 (1.6)	8	6 (4.5)	21	5 (3.7)
IMP-related AEs leading to interruption‡	6	4 (3.2)	6	4 (3.0)	9	3 (2.2)

AE, Adverse event; e, number of events; n, number of subjects with event; SAE, serious adverse event.

*Including subjects with SAEs (1 subject in the placebo group and 1 in the 20,000 JAU group).

†Including subjects with SAEs (1 subject in the 10,000 JAU group and 1 in the 20,000 JAU group) and subjects with asthma during period 2 (1 subject in the placebo group, 1 in the 10,000 JAU group, and 2 in the 20,000 JAU group).

‡Including IMP-related asthma during period 2 (1 subject in the 10,000 JAU group).

TABLE E8. Safety profile in subjects who did not use SABA due to asthma symptoms during the 14-d baseline period

Treatment group	Placebo (N = 149)		10,000 JAU (N = 142)		20,000 JAU (N = 142)	
	e	n (%)	e	n (%)	e	n (%)
SAE	3	3 (2.0)	1	1 (0.7)	4	4 (2.8)
IMP-related SAE	0	0	0	0	0	0
AE						
All	640	134 (89.9)	711	136 (95.8)	716	138 (97.2)
Mild	573	91 (61.1)	644	101 (71.1)	660	100 (70.4)
Moderate	67	43 (28.9)	67	35 (24.6)	54	36 (25.4)
Severe	0	0	0	0	2	2 (1.4)
IMP-related AE						
All IMP-related AEs	86	38 (25.5)	191	93 (65.5)	203	100 (70.4)
Mild	80	33 (22.1)	184	87 (61.3)	195	93 (65.5)
Moderate	6	5 (3.4)	7	6 (4.2)	8	7 (4.9)
Severe	0	0	0	0	0	0
Significant AEs						
Anaphylactic reaction	0	0	0	0	0	0
Asthma during period 2	36	23 (15.4)	38	20 (14.1)	36	22 (15.5)
AEs leading to discontinuation*	9	6 (4.0)	6	3 (2.1)	12	11 (7.7)
IMP-related AEs leading to interruption	7	4 (2.7)	3	3 (2.1)	2	2 (1.4)

AE, Adverse event; e, number of events; n, number of subjects with event; SAE, serious adverse event.

*Including subjects with SAEs (1 subject in the placebo group and 2 in the 20,000 JAU group) and subjects with asthma during period 2 (3 subjects in the placebo group and 4 in the 20,000 JAU group).

TABLE E9. Comparison of asthma exacerbation during period 3 with the European trial

Trial	Treatment group	No. of subjects			
		Randomized	Discontinuation during period 2	Discontinuation during period 3	With event(s) *
Japanese trial	Placebo	274	28	9	110
	10,000 JAU	274	37	8	104
	20,000 JAU	276	38	11	104
European trial ^{E4}	Placebo	277	20	48	83
	6 SQ-HDM [†]	275	38	34	62
	12 SQ-HDM [‡]	282	34	43	59

*Number of subjects with moderate or severe asthma exacerbation(s) during period 3.

[†]Equivalent to 10,000 JAU.[‡]Equivalent to 20,000 JAU.

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