ARTICLE IN PRESS

Allergology International xxx (2016) 1–9

Contents lists available at ScienceDirect

Allergology International

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

Original article

Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study

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ARTICLE INFO

Article history:
Received 18 April 2016
Received in revised form
16 May 2016
Accepted 25 May 2016
Available online xxx

Keywords:
Bilastine
Fexofenadine
H_1-antihistamine
Perennial allergic rhinitis
Total nasal symptom score

Abbreviations:
AR, allergic rhinitis; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; PET, positron emission tomography; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TSS, total symptom score; QOL, quality of life; AE, adverse event; ADR, adverse drug reaction; ECG, 12-lead electrocardiogram; FAS, full analysis set; SP, safety population; ANCOVA, analysis of covariance; ANOVA, analysis of variance; SD, standard deviation; SE, standard error; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; SAS, statistical analysis software; MCID, minimal clinically important difference

ABSTRACT

Background: Bilastine, a novel non-sedating second-generation H_1 antihistamine, has been approved in most European countries since 2010. This study aimed to evaluate the superiority of bilastine over placebo in Japanese patients with perennial allergic rhinitis (PAR).
Methods: This randomized, double-blind, placebo-controlled, parallel-group, phase III study (trial registration number JapicCTI-142600) evaluated the effect of a 2-week treatment period with bilastine (20 mg once daily), fexofenadine (60 mg twice daily), or a matched placebo (double dummy) in patients with PAR. All patients were instructed to record individual nasal and ocular symptoms in diaries daily. The primary endpoint was the mean change in total nasal symptom scores (TNSS) from baseline to Week 2 (Days 10–13).
Results: A total of 765 patients were randomly allocated to receive bilastine, fexofenadine, or placebo (256, 254, and 255 patients, respectively). The mean change in TNSS from baseline at Week 2 was significantly decreased by bilastine (−0.98) compared to placebo (−0.63, $P = 0.023$). Bilastine and fexofenadine showed no significant difference in the primary endpoint. However, the mean change in TNSS from baseline on Day 1 was more significantly decreased by bilastine (−0.99) than by placebo (−0.28, $P < 0.001$) or fexofenadine (−0.62, $P = 0.032$). The active drugs also improved instantaneous TNSS 1 h after the first and before the second drug administration on Day 1 ($P < 0.05$). The study drugs were well tolerated.
Conclusions: After 2-week treatment period, bilastine 20 mg once daily was effective and tolerable in Japanese patients with PAR, and exhibited a rapid onset of action.
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Introduction

Allergic rhinitis (AR) is one of the most common diseases in worldwide. In the Practical Guideline for the Management of Allergic Rhinitis in Japan,[1,2] AR has been classified as seasonal or

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.05.014
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perennial (SAR and PAR, respectively) depending on the temporal pattern of exposure to a triggering aeroallergens and duration of symptoms. SAR is associated with a wide variety of pollen allergens including Japanese cedar pollen and, thus, depends on the geographic location and climatic conditions, whereas PAR is most frequently caused by *Dermatophagoides* allergens (a major antigen in house dust or mites) in Japan.[2,3] AR is a global health problem that affects 10%–30% of the population.[4,5] In 2008, the prevalence rates of PAR, SAR, and AR were 23.4%, 29.8%, and 39.4%, respectively in the Japanese population.[1] The pathological characteristics of both PAR and SAR are a type I allergic disease of the nasal mucosa with associated nasal symptoms such as sneezing and rhinorrhea, as well as nasal congestion or itching. AR symptoms are induced by several chemical mediators released from the mast or inflammatory cells and histamine is a particularly important mediator of AR symptoms, especially sneezing, rhinorrhea, and nasal itching. Oral H_1-antihistamines are symptomatic treatment used to alleviate the symptoms and associated discomfort of AR in everyday life. Newer second-generation H_1-antihistamines are highly selective for the H_1 receptor, and their penetration of the central nervous system is limited. Therefore non-sedating, second-generation H_1-antihistamines are the recommended drug therapy for AR in the present guidelines.[1,5,6] The advantages of oral H_1-antihistamines include rapid onset of action, once-daily dosing, and maintenance of efficacy with regular use.[5]

Bilastine is a novel non-sedating second-generation H_1-antihistamine, which has been approved for the symptomatic treatment of AR and urticaria in numerous countries (Europe, Central/South America, and Africa).[7] It is a potent and highly selective H_1-antihistamine[8] with a good safety profile.[9] Studies in healthy volunteers and patients have shown that bilastine does not affect cardiac conduction[10] or driving ability,[11] satisfied positron emission tomography (PET) criteria to be defined as a non-sedating antihistamine,[12] is not substantially metabolized in humans,[13] and can be safely administered to patients with different degrees of renal insufficiency without the need for dose adjustments.[14] In clinical studies, bilastine 20 mg administered once daily exerted efficacy in AR was comparable to that of cetirizine[15] and desloratadine,[16] while its efficacy in chronic idiopathic urticaria was comparable to that of levocetirizine.[17]

This is the first study to assess the efficacy and safety of once daily bilastine 20 mg versus (vs.) a placebo in Japanese patients with PAR. In addition, the efficacy of bilastine was subsequently compared to that of fexofenadine in a reference group of patients.

Methods

Study design

We conducted a multicenter, randomized, double-blind, placebo controlled, parallel-group, pivotal Phase III study at four centers in Japan between September 2014 and January 2015. The study design, which is shown in Figure 1 consisted of observation and treatment periods. The eligible patients commenced a 2-week observational period and received placebo twice a day for at least 7 days to assess their baseline symptoms under single-blind conditions before their registration. A total of 750 patients were eventually randomly allocated (1:1:1) to one of three treatment groups, bilastine 20 mg, fexofenadine 60 mg, or placebo (double dummy). A non-deterministic minimization method with a stochastic-biased coin was used in the randomization of patients. The sum of the total nasal symptom scores (TNSS) over the 3 days before the randomization ($\geq$16, $\leq$23, and $\geq$24 points) were used as stratification factors of minimization to ensure a balance existed between the treatment groups. Furthermore, the randomization was performed centrally using a computer (ADJUST Co., Ltd., Sapporo, Japan).

The study drugs were supplied by Taiho Pharmaceutical and were administered twice a day, in the morning 1 h before or 2 h after breakfast and in the evening before or after dinner during the observation and treatment periods (Supplementary Table 1). A follow-up visit was scheduled 4–7 days after the end of the treatment. The patients who completed all of their visits were considered to have completed the study while those who were assigned to a treatment and discontinued the study before the completion had an early withdrawal visit to assess the safety and efficacy at the end of the treatment.

Patients

Patients were considered eligible for inclusion in the study if they met the following eligibility criteria: aged 18–74 years, diagnosed with a 2-year or longer history of PAR, and had a positive nasal provocation test with house dust disc and specific

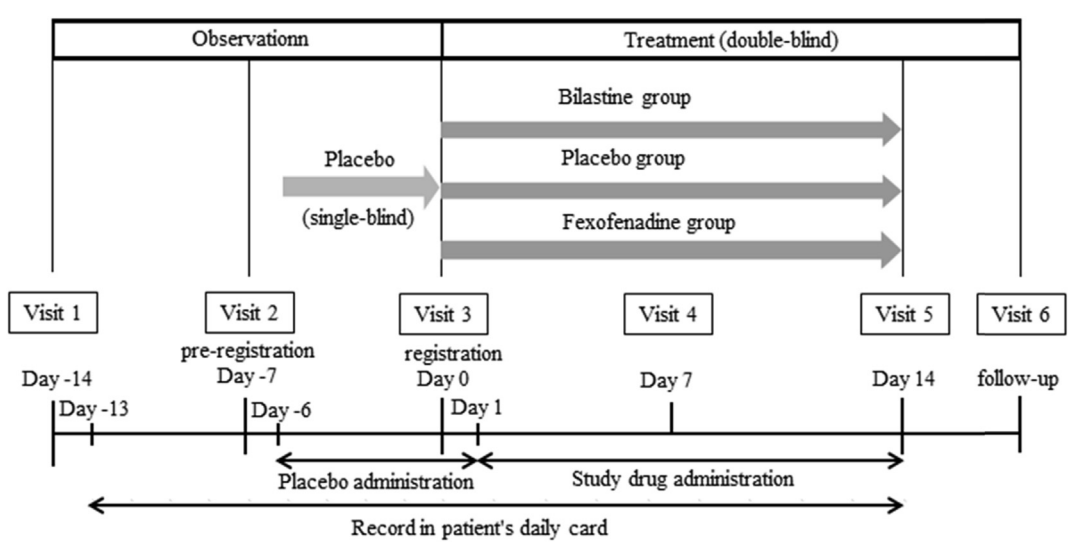

Fig. 1. Study design.

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immunoglobulin E (IgE) antibody tests to PAR allergens (i.e., positive to at least one house dust mite, *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*) and were subsequently preregistered. The inclusion criteria for patient registration were: a TNSS sum of ≥16 (up to 45 points) and a sum of rhinorrhea or sneezing scores of ≥5 (up to 12 points) for 3 days before randomization, appropriately recorded symptom scores in the patient diary during the last 3 days before both the preliminary registration and registration, and an 80% or higher rate of both symptom score entry in the patient diary and compliance during the observation period of the registration.

Patients were excluded from the study if they had active infections; nasal septal ulcers or polyps, and asthma, as well as any other nasal, ocular, or ear disorders that could interfere with the efficacy evaluation (vasomotor, eosinophilic, acute/chronic, hypertrophic, and drug-induced rhinitis, as well as viral conjunctivitis, otitis media, sinusitis, nasal polyps, repetitive nasal hemorrhage, and treatment-requiring nasal septal deviation); a previous history of intranasal surgery (such as laser therapy, coagulative necrosis, and resection); specific immunotherapy (such as cedar pollen sublingual immunotherapy for cedar pollinosis); or non-specific modulation therapy in the previous 3 years; underwent immunotherapy or received corticosteroid injections or treatment with humanized anti-IgE antibody (omalizumab) in the previous 180 days; taken other investigational drugs in the previous 90 days; received corticosteroids or P-glycoprotein inhibitors in the previous 30 days; taken anti-allergic, antihistamine, anticholinergic, nasal/ocular vasoconstrictor, non-prescription, or aluminum hydroxide/magnesium hydroxide drugs in the previous 7 days before study commencement. Furthermore, patients with a nasal congestion score of 4 on at least 1 of the 3 days prior to registration; a daily TNSS variation above 3 during the 3 days prior to registration; and a 3-day total TNSS before the randomization that had reduced by 40% or more from total obtained 3 days before pre-registration were also excluded. Similarly, patients who did not respond to treatment with the usual antihistamine dose for PAR were excluded.

Efficacy assessments

The primary efficacy endpoint was the mean change in TNSS from baseline at Week 2 (4 days: Days 10–13). The TNSS is the sum of the individual scores for rhinorrhea, sneezing, and nasal congestion and itching. The patients were instructed to record their symptom scores (individual nasal and ocular symptoms) in the patient diary daily during the observation and treatment periods. The baseline values were the average scores during the 4 consecutive days prior to the day of drug administration (Day −3 to 0). The secondary efficacy variables were the total ocular symptom score (TOSS), total symptom score (TSS), individual nasal and ocular symptom scores, instantaneous TNSS on Day 1, quality of life (QOL) score using the Japanese Allergic Rhinitis QOL Standard Questionnaire No. 1[1], rhinoscopic findings, and degree of patient satisfaction with treatment.

The sneezing, rhinorrhea or nasal congestion was evaluated using five-point scale according to the Japanese Guideline.[1] The nasal itching score was based on a four-point scale: nasal itching with frequent nose rubbing and blowing, 3; a nasal itch with occasional nose rubbing and blowing, 2; a nasal itch that was not persistent, 1; and no symptoms, 0. The severity of ocular symptoms were scored using an individual five-point scale based on eye itching (more severe symptoms than 3, 4; frequent eye rubbing, 3; occasional eye rubbing, 2; no eye rubbing, 1; and no symptoms, 0) and lacrimation (more severe symptoms than 3, 4; frequent tear wiping, 3; occasional tear wiping, 2, no tear wiping from eyes, 1; and no symptoms, 0).

For the exploratory evaluation of the onset of action, patients monitored and scored their instantaneous nasal symptoms (rhinorrhea, sneezing, and nasal congestion and itching) using a five-point scale (no symptoms, 0; mild, 1; moderate, 2; severe, 3; and extremely severe, 4) before (baseline) and 1 h after the first drug administration and before the second drug administration on Day 1. The rhinoscopic findings included swelling or discoloration of the inferior turbinate mucosa and the quantity or properties of the nasal discharge, which were scored using a four-point scale. The degrees of satisfaction was scored on a five-point scale, which the patients used to assess their level of satisfaction with the treatment efficacy and safety (very satisfied, 5; satisfied, 4; acceptable, 3; dissatisfied, 2; and very dissatisfied, 1). The degree of satisfaction with the treatment was assessed during the last visit of the treatment period.

Safety assessments

The safety was assessed based on the incidence and severity of the adverse events (AEs), vital signs (axillary body temperature and supine blood pressure and pulse rate), laboratory tests (clinical chemistry, hematology, and urinalysis), and a 12-lead electrocardiogram (ECG). The AEs were monitored during the treatment and follow-up period. Treatment compliance was assessed through the patient diary card recording. The causal relationships between all the AEs and the drug were categorized by the investigator as probable, possible, unlikely, or unrelated.

Statistical analyses

The objective of this study was to verify the superiority of bilastine 20 mg over placebo, which was the primary efficacy endpoint for the full analysis set (FAS) population. A sample size of 678 patients (226 per group) was required to provide a statistical power of 90% at a two-sided level of significance of 5%, assuming a treatment difference of 0.75 and a standard deviation (SD) of 2.45, based on a previous study.[18] Assuming that approximately 10% of the patients might withdraw from the study, the final sample size required was calculated to be 750 patients (250 per group).

The efficacy analyses were performed for the full analysis set (FAS) of patients who were randomized to a treatment, received at least one dose of the study drug, completed the study without violating the patient inclusion and exclusion criteria protocol, and completed the diary assessment of the TNSS for at least 2 days in the study from Day 10–13.

For the primary efficacy endpoint, the superiority of bilastine 20 mg to placebo was analyzed using an analysis of covariance (ANCOVA) model including treatment as a factor with baseline and institution as a covariate. There were four participating institutions. For the secondary efficacy endpoints, the mean change from baseline in TNSS, TOSS, TSS, each symptom score, and the instantaneous TNSS on Day 1 were analyzed using the same ANCOVA model. The mean change from baseline in the daily TNSS and the QOL scores were analyzed using the Student's *t*-test. For the degree of satisfaction and rhinoscopic findings, the differences between the two treatment groups were assessed using a pairwise comparison, using the Fisher's exact or Wilcoxon two-sample tests.

The safety analyses were performed on the safety population (SP) of patients who received at least, one dose of the study drug. The incidences of AEs and adverse drug reactions (ADRs) were analyzed using the Fisher's exact tests. The AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

All the statistical analyses were performed using the statistical analysis software (SAS) version 9.2 (SAS Institute, Cary, NC, USA). All

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the reported P-values were two-sided, and a $P < 0.05$ was considered statistically significant.

Ethical approval and clinical trial registration

This trial was conducted in accordance with the World Medical Association Declaration of Helsinki and the Japanese Good Clinical Practice Guidelines. The study protocol was approved by the Institutional Review Boards of all participating institutions. Informed consent was obtained from all the participants included in the study, which was registered with the Japan Pharmaceutical Information Center (number JapicCTI-142600).

Results

Study population

A total of 1001 patients were initially screened for the study out of which 236 (23.6%) were excluded, and the remaining 765 patients were randomly allocated to three treatment groups. The groups were bilastine, fexofenadine, and placebo with 256, 254, and 255 patients, respectively (Fig. 2). The most common reason for patient exclusion was the failure to meet the eligibility criteria (222 patients, 94.1%). One patient assigned to bilastine was excluded from the safety analysis because the patient did not take a study drug. Twenty-one patients were withdrawn from the study (bilastine, five [2.0%]; placebo, seven, [2.7%], and fexofenadine, nine [3.5%]). Of the 765 randomized patients, 744 (>97%) completed the study, 747 were included in the efficacy analysis (FAS), and 764 were included in the safety analysis (SP).

The demographic and baseline characteristics of the FAS population were similar for the three groups and are summarized in Supplementary Table 2. The mean rate of treatment compliance was also similar for the three study groups (placebo, 98.95%; bilastine, 99.26%; and fexofenadine, 99.05%).

Efficacy

The result of the primary endpoint analysis revealed a mean change in the TNSS from baseline at Week 2 (Table 1) of −0.98 (95% confidence interval [CI], −1.19 to −0.77) in bilastine and −0.63 (−0.84 to −0.42) in placebo. The estimated difference in the adjusted mean between bilastine and placebo was −0.35 (−0.65 to −0.05). Because the p-value ($P = 0.023$) of the between-group statistical test was lower than the prespecified significance level of two-sided 5%, the superiority of bilastine 20 mg to placebo was confirmed. Furthermore, the secondary analysis of the primary endpoint was performed to compare the efficacy of bilastine and fexofenadine. The estimated mean change in the TNSS was −0.96 (−1.17 to −0.75) in fexofenadine, and the estimated difference in the adjusted mean between bilastine and fexofenadine was 0.00 (−0.31 to 0.31). The difference between bilastine and fexofenadine was not statistically significant in the primary endpoint ($P = 0.999$, Table 1).

The mean change in the daily TNSS from baseline during the treatment period is presented in Figure 3. The TNSS of placebo decreased gradually from baseline in a treatment day-dependent manner. The mean ± SD change in the TNSS of placebo, bilastine, and fexofenadine from baseline on Day 1 was −0.28 ± 1.67, −0.99 ± 1.87, and −0.62 ± 1.90, respectively. There were statistically significant differences between active drug

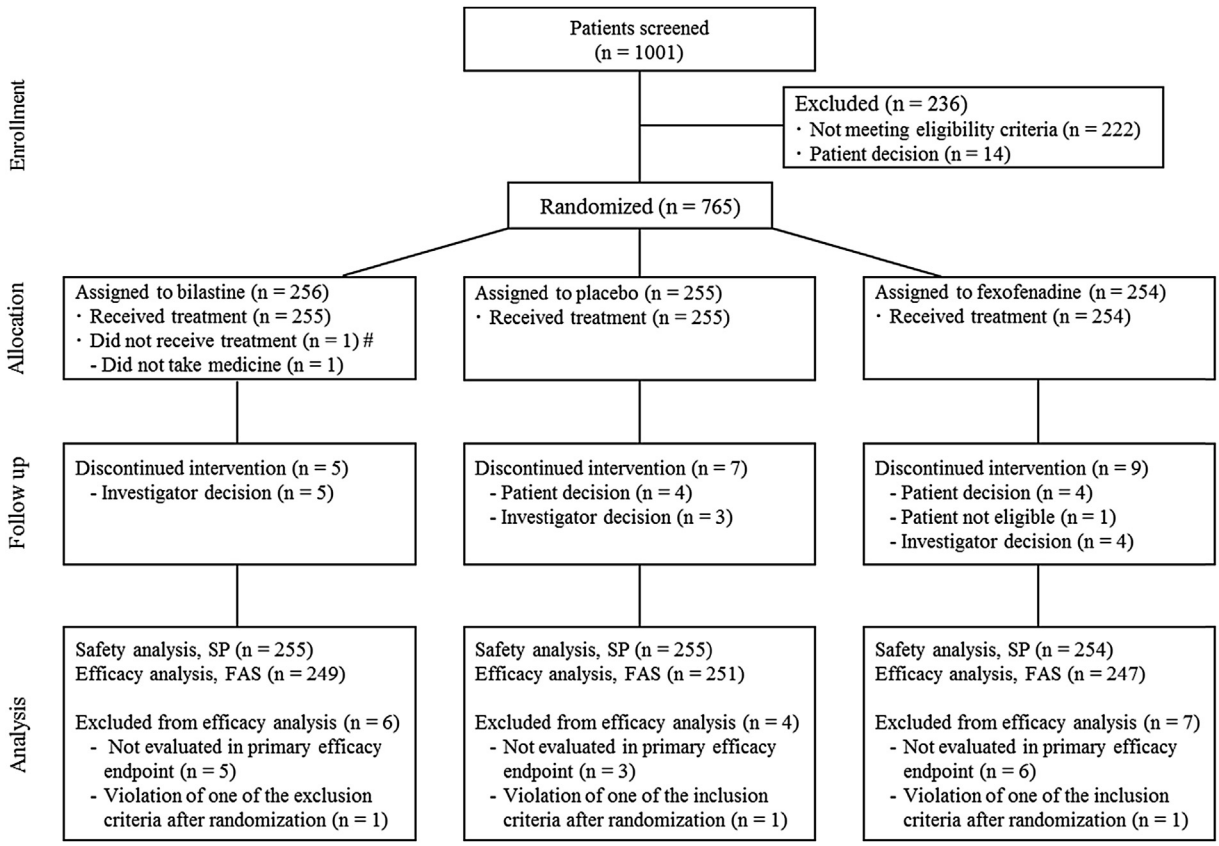

Fig. 2. Flow chart of patient enrollment and disposition. #Patient included due to discontinued intervention ($n = 5$).

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Table 1
Primary endpoint: mean change in total nasal symptom score (TNSS) from baseline at Week 2 in full analysis set (FAS).

		Placebo ($n = 251$)	Bilastine ($n = 249$)	Fexofenadine ($n = 247$)
Baseline	Mean ± SD	7.33 ± 1.49	7.48 ± 1.54	7.38 ± 1.43
Week 2	Mean ± SD	6.73 ± 1.87	6.48 ± 2.12	6.42 ± 1.97
	Estimated mean change (95% CI)	−0.63 (−0.84 to −0.42)	−0.98 (−1.19 to −0.77)	−0.96 (−1.17 to −0.75)
	Estimated mean difference†(95% CI)	–	−0.35 (−0.65 to −0.05)	−0.34 (−0.64 to −0.04)
	P-value vs. placebo	–	0.023	0.027
	Estimated mean difference††(95% CI)	–	0.00 (−0.31 to 0.31)	–
	P-value vs. fexofenadine	–	0.999	–

Analysis of covariance (ANCOVA) model including treatment as factor with baseline and institution as covariates. CI, confidence interval; estimated mean difference † = estimated mean change in bilastine or fexofenadine minus estimated mean change in placebo. Estimated mean difference†† = estimated mean change in fexofenadine minus estimated mean change in bilastine. Week 2, change in mean score for treatment period Day 10–13 (4 days) compared with baseline (for total 4 days: Day −3 to 0).

and placebo ($P < 0.05$), and the change in TNSS of bilastine was significantly greater than that of fexofenadine on Day 1 ($P = 0.032$). The mean change in the daily TNSS from baseline for bilastine showed a constant decrease from Day 1–13 (approximately −1.0). On the other hand, the mean change in the daily TNSS of the fexofenadine showed a gradual decrease until Day 3 and was similar to that of bilastine on Day 3 and after that.

Table 2 shows the estimated mean change from baseline in the TNSS and four individual nasal symptoms over the 2-week treatment period. Both bilastine and fexofenadine showed a significantly improved TNSS on Day 1–3, Week 1 (Day 4–7), compared to placebo, and there were no significant differences between bilastine and fexofenadine at any period. The results of each nasal symptom analyzed in the TNSS revealed that the mean change in rhinorrhea and nasal itching from baseline for bilastine was more significantly decreased by Day 1–3 and Week 1, compared with placebo. Bilastine also significantly improved the sneezing but not the nasal congestion at all examination periods (Day 1–3, Week 1 and 2). In the fexofenadine treatment, similar results were obtained despite the lack of improvement in the rhinorrhea at any period.

The mean change from baseline in the TOSS at Day 1–3 and Week 1 were significantly greater for bilastine than for placebo (the estimated difference [95% CI], *P*-value: −0.21 [−0.35 to −0.07] $P = 0.004$ by Day 1–3; −0.15 [−0.30 to −0.01], $P = 0.038$ by Week 1; and −0.12 [−0.27 to 0.03], $P = 0.133$ by Week 2). The mean change from baseline in TOSS by Day 1–3 and Week 1 and 2 were also significantly greater for fexofenadine than for placebo (−0.27 [−0.42 to −0.13], $P < 0.001$ by Day 1–3; −0.33 [−0.47 to −0.18], $P < 0.001$ by Week 1; and −0.30 [−0.45 to −0.15], $P < 0.001$ by Week 2). There were statistically significant differences in the TOSS between bilastine and fexofenadine by Week 1 and 2 (−0.17 [−0.32 to −0.03], $P = 0.022$ by Week 1; and −0.18 [−0.33 to −0.03], $P = 0.020$ by Week 2). The results of each ocular symptom evaluation performed for the TOSS, revealed that the mean change in eye itching from baseline was more significantly decreased by Day 1–3 as well as Week 1 and 2 for bilastine than for placebo. Fexofenadine also exhibited significant improvement in eye itching at all the examination periods compared to placebo. There were statistically significant differences in eye itching between bilastine and fexofenadine by Week 1. The improvement in lacrimation following bilastine treatment was weaker than that of the eye itching. On the other hand, fexofenadine showed a significant improvement in lacrimation at all the examination periods compared to placebo (data not shown).

Both bilastine and fexofenadine showed significantly greater improvements than placebo in the mean change from baseline in the TSS by Day 1–3 as well as Week 1 and 2 (bilastine: −0.80 [−1.16 to −0.44], $P < 0.001$ by Day 1–3; −0.51 [−0.89 to −0.13], $P = 0.009$ by Week 1; and −0.47 [−0.87 to −0.07], $P = 0.021$ by Week 2; fexofenadine: −0.65 [−1.01 to −0.29], $P < 0.001$ by Day 1–3, −0.76 [−1.15 to −0.38], $P < 0.001$ by Week 1; and −0.64 [−1.04 to −0.24], $P = 0.002$ by Week 2). There were no statistically significant differences in the TSS between bilastine and fexofenadine.

The exploratory evaluation of the onset of action was performed under natural environmental conditions by assessing the instantaneous TNSS on Day 1 (first drug administration day). Significant

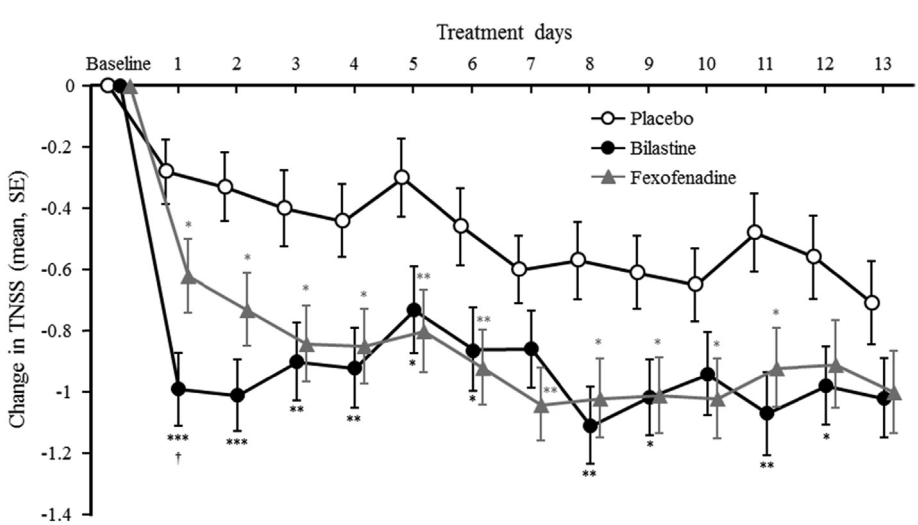

Fig. 3. Change in daily total nasal symptom score (TNSS) from baseline over treatment period in full analysis set (FAS). $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ for bilastine or fexofenadine vs. placebo (Student's *t*-test). $^{\dagger}P < 0.05$ for bilastine vs. fexofenadine (Student's *t*-test).

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Table 2
Mean change from baseline in total nasal symptom score (TNSS) by treatment period in full analysis set (FAS).

			Placebo ($n = 251$)	Bilastine ($n = 249$)	Fexofenadine ($n = 247$)
TNSS	Baseline	Mean ± SD	7.33 ± 1.49	7.48 ± 1.54	7.38 ± 1.43
	Day 1–3	Estimated mean change (95% CI)	−0.36 (−0.55 to −0.18)	−0.94 (−1.12 to −0.75)***	−0.74 (−0.92 to −0.55)**
	Week 1		−0.48 (−0.68 to −0.28)	−0.81 (−1.01 to −0.62)*	−0.91 (−1.11 to −0.72)**
	Week 2		−0.63 (−0.85 to −0.42)	−0.98 (−1.19 to −0.76)*	−0.98 (−1.19 to −0.76)*
Rhinorrhea	Baseline	Mean ± SD	2.19 ± 0.63	2.27 ± 0.62	2.25 ± 0.73
	Day 1–3	Estimated mean change (95% CI)	−0.10 (−0.16 to −0.03)	−0.30 (−0.37 to −0.23)*** †	−0.18 (−0.25 to −0.12)
	Week 1		−0.17 (−0.24 to −0.10)	−0.27 (−0.34 to −0.21)*	−0.26 (−0.33 to −0.19)
	Week 2		−0.21 (−0.29 to −0.14)	−0.30 (−0.37 to −0.22)	−0.31 (−0.39 to −0.24)
Sneezing	Baseline	Mean ± SD	1.55 ± 0.68	1.55 ± 0.66	1.50 ± 0.60
	Day 1–3	Estimated mean change (95% CI)	−0.10 (−0.15 to −0.04)	−0.24 (−0.30 to −0.18)**	−0.23 (−0.29 to −0.17)**
	Week 1		−0.10 (−0.16 to −0.04)	−0.20 (−0.26 to −0.14)*	−0.24 (−0.30 to −0.17)**
	Week 2		−0.11 (−0.17 to −0.04)	−0.23 (−0.29 to −0.16)*	−0.22 (−0.29 to −0.16)*
Nasal congestion	Baseline	Mean ± SD	1.82 ± 0.57	1.82 ± 0.61	1.82 ± 0.56
	Day 1–3	Estimated mean change (95% CI)	−0.08 (−0.14 to −0.02)	−0.12 (−0.18 to −0.06)	−0.11 (−0.17 to −0.05)
	Week 1		−0.07 (−0.14 to −0.01)	−0.11 (−0.17 to −0.05)	−0.14 (−0.20 to −0.07)
	Week 2		−0.11 (−0.18 to −0.04)	−0.18 (−0.24 to −0.11)	−0.17 (−0.24 to −0.10)
Nasal itching	Baseline	Mean ± SD	1.77 ± 0.54	1.84 ± 0.57	1.81 ± 0.55
	Day 1–3	Estimated mean change (95% CI)	−0.09 (−0.15 to −0.02)	−0.28 (−0.35 to −0.22)***	−0.21 (−0.28 to −0.15)**
	Week 1		−0.13 (−0.20 to −0.07)	−0.23 (−0.29 to −0.17)*	−0.28 (−0.34 to −0.22)**
	Week 2		−0.20 (−0.27 to −0.14)	−0.27 (−0.34 to −0.21)	−0.27 (−0.34 to −0.21)

Analysis of covariance (ANCOVA) model including treatment as factor with baseline and institution as covariates. CI, confidence interval, SD, standard deviation; *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for bilastine/fexofenadine vs. placebo. †$P < 0.05$ for bilastine vs. fexofenadine. Day 1–3, change in mean score for the treatment period Day 1–3 (3 days) compared with baseline (for total 4 days: Days −3 to 0). Week 1, change in mean score for treatment period Day 4–7 (4 days) compared with baseline (for total 4 days: Day −3 to 0). Week 2, change in mean score for treatment period Day 10–13 (4 days) compared with baseline (for total 4 days: Days −3 to 0).

differences were observed in the mean change from baseline for the instantaneous TNSS 1 h after the first drug administration between the active treatment and placebo, which were maintained up to the second drug administration on Day 1 (Table 3).

For overall satisfaction with treatment, the percentages of patients who responded with very satisfied or satisfied during the last evaluation were 43.8% (109/249), 31.2% (78/250), and 43.7% (108/247) for bilastine, placebo, and fexofenadine, respectively. Both bilastine and fexofenadine showed a statistically significant difference in the percentage of patients who responded as very satisfied or satisfied compared to placebo ($P = 0.004$). Moreover, there was no significant difference between bilastine and fexofenadine (Fig. 4). The rhinoscopic findings and QOL scores were not significantly improved by the active treatments compared with placebo (data not shown).

Safety

The safety analyses were conducted in the SP, which consisted of 764 patients. The AEs or ADRs reported during the study were mild or moderate in severity and were similar in type and incidence in the three study groups (AEs: placebo, 4.7%; bilastine, 7.5%; and fexofenadine, 5.5%; ADRs: placebo, 0.8%; bilastine, 2.0%; and fexofenadine, 2.0%). The proportion of patients who experienced at least one AE and ADR were similar for all the groups (Table 4, Fisher's test; AEs: placebo vs bilastine, $P = 0.266$; placebo vs fexofenadine, $P = 0.693$; and bilastine vs fexofenadine, $P = 0.472$; ADRs: placebo vs bilastine, $P = 0.450$; placebo vs fexofenadine, $P = 0.285$; and bilastine vs fexofenadine, $P = 1.000$). There was no AE with a 2% or higher incidence in any of the groups. The AEs were categorized using the System Organ Class of nervous system disorders, and no patient reported any in placebo while two patients (0.8%) in bilastine and one (0.4%) in fexofenadine reported somnolence. In addition, one patient (0.4%) in bilastine and two (0.8%) in fexofenadine reported headaches; dizziness postural was reported in one patient (0.4%) in bilastine while one patient (0.4%) in fexofenadine reported dizziness. There were no serious AEs or deaths, and no patients withdrew from the study because of AEs. ADRs were reported by five patients (2.0%) each in bilastine and fexofenadine and two (0.8%) in placebo. There were no clinically significant changes in any laboratory test, ECGs, and vital signs from baseline values in any of the treatment groups.

Table 3
Mean change from baseline in instantaneous total nasal symptom score (TNSS) 1 hour after first study drug administration and immediately before second study drug administration in full analysis set (FAS).

		Placebo	Bilastine	Fexofenadine
Baseline	n	250	249	246
	Mean ± SD	6.0 ± 2.4	6.1 ± 2.3	6.4 ± 2.6
1 hour after first study drug administration	n	250	248	246
	Estimated mean change (95% CI)	−1.2 (−1.4 to −1.0)	−1.5 (−1.7 to −1.3)*	−1.6 (−1.8 to −1.4)**
Immediately before second study drug administration	n	245	249	245
	Estimated mean change (95% CI)	−0.9 (−1.2 to −0.7)	−1.4 (−1.6 to −1.1)**	−1.5 (−1.8 to −1.3)**

Analysis of covariance (ANCOVA) model including treatment as factor with baseline and institution as covariates. CI, confidence interval, SD, standard deviation; *$P < 0.05$ and **$P < 0.01$ for bilastine or fexofenadine vs. placebo.

Please cite this article in press as: Okubo K, et al., Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study, Allergology International (2016), http://dx.doi.org/10.1016/j.alit.2016.05.014

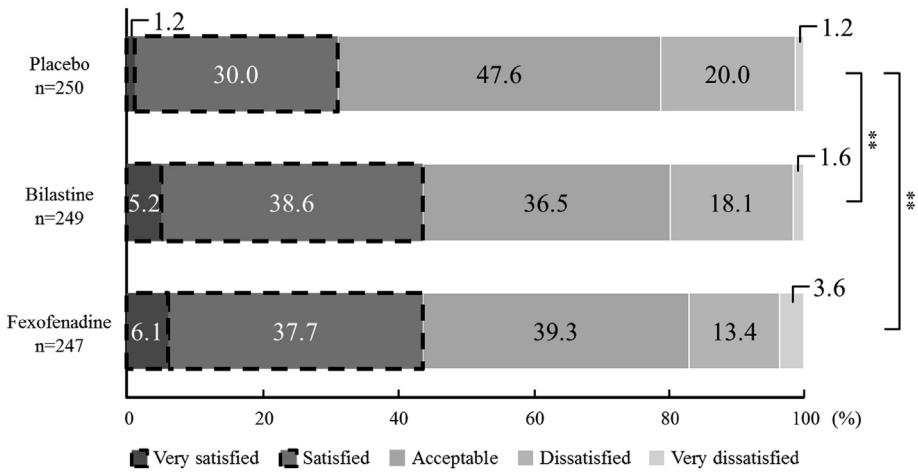

Fig. 4. Degree of satisfaction with treatment in full analysis set (FAS). $^{**}P < 0.01$; Percentage of patients who were satisfied or very satisfied was compared between placebo and bilastine or fexofenadine (Fisher's exact test).

Discussion

This pivotal phase-III study was the first to evaluate the efficacy and safety of bilastine in Japanese patients with PAR. The results of the primary endpoint analysis revealed that bilastine significantly improved the TNSS by Week 2 compared with placebo, suggesting that the efficacy of bilastine 20 mg administered once daily for 2 weeks was verified to be significantly better than placebo. Following the confirmation of the superiority of bilastine over placebo, the difference between the efficacy of bilastine and the reference drug fexofenadine 60 mg twice daily was evaluated using the primary endpoint. The result showed that fexofenadine significantly decreased the TNSS by Week 2, and there was no significant difference between the active treatments, indicating that efficacy of bilastine 20 mg once daily was comparable to that of fexofenadine 60 mg twice daily.

While it is important to make informed decisions in clinical trials based on statistical significance, the clinical significance or clinically meaningful differences should also be considered. One objective approach to determining the clinical significance involves applying the concept of a minimal clinically important difference (MCID), which is defined as the smallest change in a given outcome that is meaningful to a patient.[19] Higaki *et al.*[20] first reported that calculating the MCIDs for symptoms and QOL scores in Japanese cedar/cypress pollinosis using the anchor-based approach. However, to the best of our knowledge, an MCID for PAR has not been previously determined in Japan. We considered the clinical meaningfulness for the estimated mean difference from placebo at −0.35 (95% CI, −0.65 to −0.05) in the bilastine treatment by comparing with the previous results of intranasal corticosteroid in Japanese patients with PAR. Okubo *et al.*[21] reported that fluticasone furoate nasal spray (FFNS) once daily in a dose of 110 μg significantly decreased in change of TNSS from baseline, compared with placebo (the adjusted mean difference from placebo: −1.119 [95% CI, −1.85 to −0.39]). Since the rating nasal symptoms score was different among studies (5-point vs. 4-point scale), % reduction of the adjusted mean difference from placebo at 2 weeks treatment period in each drug against the adjusted mean change in TNSS from

Table 4
Adverse events (AEs) and adverse drug reactions (ADRs) reported over 2-week treatment period in safety population (SP).

	Placebo ($n = 255$)		Bilastine ($n = 255$)		Fexofenadine ($n = 254$)	
	n (%)	95%CI (%)	*n* (%)	95%CI (%)	*n* (%)	95% CI (%)
Patients reporting ≥1 AE	12 (4.7)	2.5–8.1	19 (7.5)	4.5–11.4	14 (5.5)	3.0–9.1
Incidence of AE†						
≥2% in any treatment group	0	–	0	–	0	–
Withdrawals due to AEs	0	–	0	–	0	–
Serious AEs	0	–	0	–	0	–
Nervous system disorders††	0 (0.0)	0.0–1.4	4 (1.6)	0.4–4.0	4 (1.6)	0.4–4.0
Dizziness†	0 (0.0)	0.0–1.4	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2
Dizziness postural†	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2	0 (0.0)	0.0–1.4
Headaches†	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2	2 (0.8)	0.0–2.8
Somnolence†	0 (0.0)	0.0–1.4	2 (0.8)	0.1–2.8	1 (0.4)	0.0–2.2
Patients reporting ≥1 ADR	2 (0.8)	0.1–2.8	5 (2.0)	0.6–4.5	5 (2.0)	0.6–4.5
Gastrointestinal disorders††	1 (0.4)	0.0–2.2	1 (0.4)	0.0–2.2	1 (0.4)	0.0–2.2
Investigations††	1 (0.4)	0.0–2.2	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2
Nervous system disorders††	0 (0.0)	0.0–1.4	2 (0.8)	0.1–2.8	3 (1.2)	0.2–3.4
Dizziness†	0 (0.0)	0.0–1.4	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2
Headaches†	0 (0.0)	0.0–1.4	0 (0.4)	0.0–1.4	1 (0.4)	0.0–2.2
Somnolence†	0 (0.0)	0.0–1.4	2 (0.8)	0.1–2.8	1 (0.4)	0.0–2.2
Respiratory, thoracic and mediastinal disorders††	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2	0 (0.0)	0.0–1.4
Skin and subcutaneous tissue disorders††	0 (0.0)	0.0–1.4	1 (0.4)	0.0–2.2	0 (0.0)	0.0–1.4

CI, confidence interval; †MedDRA (ver. 17.1) Preferred Term; ††MedDRA (ver. 17.1) System Organ Class.

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baseline for placebo (−0.63 in this study vs. −1.71 in FFNS study) was calculated. As the results, the % reduction of the adjusted mean difference from placebo was 56% (95%CI, 8–103%) for bilastine 20 mg, 65% (95%CI, 23–108%) for FFNS, respectively. It has been generally known that the efficacy of intranasal corticosteroids is stronger than that of H_1-antihistamines,[22] therefore, it could be considered that there were clinically meaningful differences in the change in TNSS from baseline at Week 2 for both bilastine and fexofenadine compared to placebo in the present study.

The mean changes in the daily TNSS from baseline for the active treatments were almost significantly different from placebo during the treatment period. The mean changes in the daily TNSS showed a largely similar trend from Day 3–13 for the active treatments, however, the change in TNSS of bilastine was significantly greater than that of fexofenadine was on Day 1. On the other hand, there was no significant difference between bilastine and fexofenadine in the instantaneous TNSS on Day 1. The daily TNSS reflectively assessed the four nasal symptoms, which were rated daily by the patients using a 0–4 (3, nasal itching) grading scales. The grading of sneezing, rhinorrhea, and nasal congestion and itching were evaluated based on the frequency of sneezing (number/day), the frequency of nasal blowing (number/day), duration of mouth-breathing, and duration of nose itching, respectively. The instantaneous TNSS were assessed by the patients using the same nasal symptoms rated on a 0–4 (absent–very severe) grading scale at predefined times after dosing (1 and approximately 12 h in the present study). The assessment of the reflective and instantaneous symptoms scoring is recommended by regulatory authorities. The reflective symptom scores assess the overall degree of effectiveness over a prespecified time interval, whereas the instantaneous scores assess the effectiveness at the end-of-dosing interval.[23] The assessment of the instantaneous symptom scores is usually used to evaluate the efficacy of study drugs in environmental exposure chamber studies in Japan.[24,25] Therefore, there were no critical issues regarding the method used for rating the symptoms scores, as well as for the evaluation performed based on symptom severity and timing under natural environmental conditions. Moreover, this study was a double-blind, placebo-controlled study. Based on these observations, it might be concluded that the instantaneous TNSS could be appropriate for evaluating the onset of action under natural environmental conditions, despite the fact that the first clinical study was performed without validation. The difference between the daily and instantaneous TNSS values on Day 1 between the active treatment groups could not be clearly determined based on the existing factors. However, it might have been caused by differences in the grading scales used for both the daily and instantaneous TNSS evaluations. Nevertheless, the active treatments significantly improved both the daily and instantaneous TNSS on Day 1 compared with those of placebo. Furthermore, considering the rapid onset of action (1 h after dosing), both bilastine 20 mg once daily and fexofenadine 60 mg twice-daily maintained their efficacy over the course of one day under natural environmental conditions in Japanese patients with PAR.

As shown in the daily TNSS results, the mean change in TNSS and individual nasal symptom score (except nasal congestion) from baseline at Day 1–3 as well as Week 1 and 2 was almost significantly improved following bilastine treatment compared with placebo. This result suggests that the efficacy of bilastine for the treatment of nasal symptoms except for congestion was maintained during the treatment period. Similar results were obtained for fexofenadine, although improvement in the rhinorrhea was not observed. Therefore, the difference in effects of bilastine and fexofenadine on rhinorrhea might be related to the significant difference observed in their mean change in daily TNSS from baseline on Day 1, despite the lack of difference in their onset of action. However, we couldn't clearly explain to why change in TNSS of bilastine was significantly greater than that of fexofenadine on Day 1, further experiments will be necessary to clarify it from the pharmacologic point of view.

The mean change from baseline in TOSS on Day 1–3 and Week 1 was significantly greater for bilastine than it was for placebo; however, there were statistically significant differences in TOSS between bilastine and fexofenadine by Week 1 and 2. Bilastine significantly improved eye itching but not lacrimation compared to placebo. On the other hand, fexofenadine significantly improved both eye itching and lacrimation during the treatment period. The efficacy of bilastine 20 mg once daily in the treatment of ocular symptoms including lacrimation (tearing in this report) in SAR has been demonstrated in three overseas clinical studies.[26] However, the efficacy of bilastine on lacrimation symptoms was weaker than that of fexofenadine in this present study. Further studies would be needed to confirm the efficacy of bilastine on ocular symptoms for Japanese patients with AR including SAR.

Both bilastine and fexofenadine showed significantly greater improvements in the TSS on Day 1–3, as well as Week 1 and 2 than placebo did. Moreover, they showed a statistically significant difference in the percentage of patients that responded very satisfied or satisfied compared with placebo. There was no significant difference in the TSS and overall satisfaction with treatment between the active treatments. Furthermore, the rhinoscopic findings and QOL scores were not significantly improved by the active treatments compared with placebo.

Although glucocorticoid nasal spray was reported to improve the rhinoscopic finding in a randomized, placebo-controlled study in Japanese adult patients with PAR,[21] to the best of our knowledge, the efficacy of oral H_1-antihistamines has not been fully elucidated. We could not provide a precise explanation for the inability of both active treatments to improve the rhinoscopic findings and QOL scores. However, both bilastine and fexofenadine have lower anti-inflammatory activity than glucocorticoid nasal spray does, which might be needed for long-term treatment periods of up to 2 weeks.

Regarding safety, there was no difference in the incidence of AEs or ADRs between bilastine, placebo, and fexofenadine. The incidence of nervous system disorders, which are a classical side effect of antihistamines, was 0%, 1.6%, and 1.6% for placebo, bilastine, and fexofenadine, respectively. There was no difference in the incidence of nervous system disorders between bilastine and fexofenadine. Furthermore, no patients withdrew from this study because of AEs, and no noteworthy events were observed compared with the ADRs reported in an overseas study.[7]

The limitations of this study include the 2-week treatment period, which may have been too short to simulate actual clinical setting conditions. There were no concerns in the safety evaluation in a 1-year administration study conducted overseas.[18] However, a long-term administration study would be required to evaluate the safety and efficacy of bilastine in Japanese patients with AR.

In conclusion, the results of the present study suggest that bilastine 20 mg administered once daily for 2 weeks was an effective and tolerable for Japanese patients with PAR. Furthermore, bilastine showed a rapid onset of action (1 h) and the associated change in TNSS was significantly greater than that of fexofenadine on Day 1. The pharmacotherapeutic characteristics of bilastine 20 mg once daily for the symptomatic treatment of PAR were similar to those of fexofenadine 60 mg administered twice daily in the present study.

Acknowledgments

The authors gratefully acknowledge Drs. Lourdes Azcárate, Román Valiente, and Luis Labeaga (Faes Farma, S.A., Spain) for their scientific review of the manuscript. The authors would also like to

thank all the appropriate parties at Quintiles Transnational Japan K.K. Tokyo and Osaka for the management, monitoring, and analysis of the data. This study was funded by the Taiho Pharmaceutical Co., Ltd., Tokyo, Japan.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.05.014.

Conflict of interest

KO received adviser fees from Taiho Pharmaceutical. MT, AS, and TH are employees of Taiho Pharmaceutical. The rest of the authors have no conflict of interest.

Authors' contributions

KO, who is a medical adviser, gave advice with the study design, conduct of the study, and interpretation of the data. MG, MA, YN, and YO who were the principal investigators of this study, contributed to the conduct of the study and data collection. MT, AS, and TH contributed to the study concept and design, the conduct of the study, and data analysis and interpretation. All the listed authors were involved in the critical review and revision of the manuscript and approved the final content.

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Supplementary Table 1. Daily schedule of study drug administration.

Observation period		Treatment period		
Morning	Evening	Treatment group	Morning	Evening
Placebo (B) Placebo (F)	Placebo (B) Placebo (F)	Bilastine	**Bilastine 20mg** Placebo (F)	Placebo (B) Placebo (F)
		Placebo	Placebo (B) Placebo (F)	Placebo (B) Placebo (F)
		Fexofenadine	**Fexofenadine 60mg** Placebo (B)	**Fexofenadine 60mg** Placebo (B)

Placebo (B), bilastine placebo tablet; Placebo (F), fexofenadine placebo tablet.

Supplementary Table 2. Patient demographic and characteristics at baseline in full analysis set (FAS).

Variable		Placebo (*n*=251)	Bilastine (*n*=249)	Fexofenadine (*n*=247)	*P-value*
Sex (males) [n (%)]		112 (44.6)	116 (46.6)	116 (47.0)	0.852
Age (years) [mean ± SD]		34.4 ± 10.1	35.9 ± 10.9	36.1 ± 10.4	0.161
BMI (kg/m2) [mean ± SD]		22.00 ± 3.33	21.54 ± 3.07	21.76 ± 3.33	0.282
Duration of PAR (months) [mean ± SD]		239.8 ± 118.5	260.1 ± 132.7	253.7 ± 122.5	0.179
TNSS [mean ± SD]		7.33 ± 1.49	7.48 ± 1.54	7.38 ± 1.43	0.520
TOSS [mean ± SD]		2.09 ± 1.44	1.99 ± 1.38	2.08 ± 1.32	0.669
TSS [mean ± SD]		9.42 ± 2.45	9.47 ± 2.46	9.46 ± 2.18	0.964
Classification of the severity of allergic rhinitis symptoms [n (%)]	Most severe	4 (1.6)	3 (1.2)	9 (3.7)	0.508
	Severe	49 (19.6)	52 (20.9)	52 (21.1)	
	Moderate	159 (63.6)	162 (65.1)	152 (61.8)	
	Mild	38 (15.2)	32 (12.9)	33 (13.4)	
	No symptoms	0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidity with seasonal allergic rhinitis [n (%)]		152 (60.6)	149 (59.8)	160 (64.8)	NA

BMI, body mass index; NA, not applicable; PAR, perennial allergic rhinitis; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TSS, total symptom score. Sex was compared between treatments using Fisher's exact test. Age, BMI, duration of PAR, TNSS, TOSS, and TSS were compared using analysis of variance (ANOVA). Classification of severity of allergic rhinitis symptoms was compared using Kruskal-Wallis test.