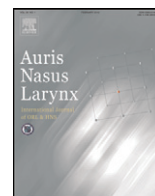




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Long-term safety and efficacy of bilastine following up to 12 weeks or 52 weeks of treatment in Japanese patients with allergic rhinitis: Results of an open-label trial

Kimihiro Okubo^{a,*}, Minoru Gotoh^b, Michinori Togawa^c, Akihiro Saito^c, Yoshihiro Ohashi^d

^a Department of Otolaryngology-Head and Neck Surgery, Nippon Medical School, Tokyo, Japan

^b Department of Otolaryngology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

^c Clinical Development Division, TAIHO Pharmaceutical Co., Tokyo, Japan

^d Ohashi ENT & Allergic Clinic, Osaka, Japan

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ABSTRACT

Objective: Bilastine is a novel second-generation antihistamine. This open-label, single-arm, phase III study evaluated the safety and efficacy of long-term treatment with bilastine in Japanese patients with seasonal (SAR) or perennial allergic rhinitis (PAR).

Methods: Patients with SAR or PAR who met the registration criteria and did not violate the exclusion criteria received bilastine (20 mg, once daily) for 12 weeks (treatment period). Patients with PAR who met the transition criteria could elect to continue the bilastine treatment for an additional 40 weeks (continuous treatment period; a total of 52 weeks). Safety and tolerability were the primary outcomes, and the main secondary endpoint was to evaluate changes in efficacy variables from baseline measurements.

Results: Fifty-eight patients with SAR and 64 patients with PAR received bilastine (20 mg/day) for 12 weeks. Fifty-five patients with PAR transitioned to the continuous treatment period. Adverse events (AEs) were reported by 17.2% of patients with SAR and by 31.3% of patients with PAR, and adverse drug reactions (ADRs) were reported by 6.3% of patients with PAR but by no patients with SAR during the 12-week treatment period. All of the ADRs were mild in severity. During the 52-week treatment period, AEs and ADRs were reported by 73.4% and 6.3% of patients with PAR, respectively. All of the ADRs occurred during the 12-week treatment period, and none during the continuous treatment period. The AEs were categorized using the System Organ Class of nervous system disorders; 4.7% of patients reported headache, but none reported somnolence. One serious AE was reported, but it was considered to be unrelated to the bilastine treatment. There were no deaths, and no patients withdrew from the study because of AEs. In patients with SAR, bilastine significantly decreased the total nasal symptom score (TNSS), total ocular symptom score (TOSS), and total symptom score (TSS) relative to baseline. Prolonged treatment with bilastine resulted in the maintenance of a significant reduction in TNSS, TOSS, and TSS from the baseline in patients with PAR. Improvement of quality of life was also observed in patients with SAR and PAR.

* Corresponding author at: Department of Otorhinolaryngology-Head and Neck Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan. Tel.: +81 3 3822 2132; fax: +81 3 5814 6207.

E-mail address: ent-kimi@nms.ac.jp (K. Okubo).

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Conclusion: Bilastine was safe, well tolerated, and effective for patients with SAR and PAR. The observed improvement was maintained for the duration of the study, with no loss of drug efficacy (registration number JapicCTI-142622).

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1. Introduction

Allergic rhinitis (AR) is a global health problem that affects 10–30% of adults and up to 40% of children [1]. AR is classified as seasonal (SAR) or perennial (PAR) depending on the temporal pattern of exposure to triggering aeroallergens and the duration of symptoms [2]. In Japan, SAR can be triggered by a wide variety of pollen allergens, including cedar, cypress, and grass pollen. The morbidity of SAR depends on the geographic region, the pollen season, and the local climate. Approximately 26.5% of the Japanese population is known to suffer from Japanese cedar (JC) pollinosis in Japan [2]. JC or cypress pollen dispersal starts in early February, reaches a peak in March–April, and finishes in May. Consequently, individuals with JC pollinosis endure allergic symptoms for at least 12 weeks. PAR is most frequently caused by dust mites and animal dander. Patients with PAR endure allergic symptoms throughout the year; 23.4% of the Japanese population was reported to suffer with PAR in 2008 [2].

In the Practical Guideline for the Management of Allergic Rhinitis in Japan [2], the severity of AR is classified as mild, moderate, and severe/very severe. In addition, nasal symptoms are classified as sneezing/nasal discharge, nasal obstruction, or complete, based on the severity of the respective nasal symptoms. The severity and duration of the symptoms of AR vary in different patients. The most effective first-line drugs for AR are second-generation antihistamines and intranasal corticosteroids [2,3]. Second-generation antihistamines are recommended for relief of sneezing and rhinorrhea symptoms in both SAR and PAR. For relief of nasal blockage or combined symptoms, leukotriene receptor antagonists or prostaglandin D₂/thromboxane A₂ receptor antagonists are recommended. Concomitant use with intranasal corticosteroids is also recommended, as needed, for both types of symptoms regarding the severity. To determine the short-term and long-term prognoses of patients receiving drug therapy, observation periods of at least 2–4 weeks and 1–3 months, respectively, are required [4].

Second-generation antihistamines are H₁-receptor antagonists with high efficacy (rapid onset of action for AR symptoms, sometimes even for nasal congestion, improvement of quality of life [QOL], and additional anti-allergic effects) and safety (low sedation rates) [5]. Because antihistamines are used to treat non-life threatening conditions, these medications should be very well tolerated and free of serious and potential safety issues for use in long-term treatment [6,7].

Bilastine, a novel second-generation antihistamine, has been granted marketing authorization for adults and adolescents (≥12 years) in most European countries since 2010. The recommended dose is 20 mg once a day for symptomatic treatment of allergic rhinoconjunctivitis and urticaria [8]. We

previously conducted a randomized, double-blind, placebo-controlled, parallel-group, phase III study to evaluate the effect of a 2-week treatment period with bilastine in Japanese patients with PAR. We demonstrated that bilastine (20 mg, once daily) was effective and well tolerated in Japanese patients with PAR, and exhibited a rapid onset of action [9]. The International Conference on Harmonisation (ICH) guidelines state that long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year [10]. Accordingly, long-term safety data on treatment with bilastine at 20 mg/day for 1 year were obtained in an overseas clinical trial [11]; however, the safety and efficacy of long-term treatment with bilastine have not been elucidated in Japanese patients with SAR or PAR. To this end, we conducted this open-label phase III study to assess the long-term safety and efficacy of bilastine following 12 or 52 weeks of treatment in Japanese patients with SAR or PAR, respectively.

2. Subjects and methods

2.1. Patients

Patients with SAR (JC pollinosis) were considered eligible for inclusion in the study at the screening visit if they met the following criteria: aged 18–74 years, with at least a 2-year history of JC pollinosis during the JC or cypress pollen season. The inclusion criteria for registration were as follows: positive for specific immunoglobulin E (IgE) antibodies to both JC and cypress allergens, a total nasal symptom score (TNSS) of ≥24 (up to 45 points), and a sum of rhinorrhea or sneezing scores of ≥6 (up to 12 points) for 3 days before registration.

The inclusion criteria for patients with PAR at the screening visit were as follows: aged 18–74 years, with at least a 2-year history of PAR, and a positive nasal provocation test with a house dust disc. The inclusion criteria for registration were: positive for specific IgE antibodies to PAR allergens (i.e., positive for at least one house dust mite, *Dermatophagoides pteronyssinus* or *D. farinae*), 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 registration.

Patients (PAR and SAR) were excluded from the study if they had active infections; nasal septal ulcers or polyps, asthma, or any other nasal, ocular, or ear disorders that could interfere with the efficacy evaluation; had undergone specific immunotherapy or non-specific modulation therapy in the previous 3 years; had undergone 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; or taken anti-allergic, antihistamine, anticholinergic,

nasal/ocular vasoconstrictors, or non-prescription drugs in the previous 7 days. Furthermore, patients with PAR were also excluded if they had 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 observation period; were positive for specific IgE antibodies against pollen antigens (JC, cypress, orchardgrass, mugwort, or ragweed) entering the treatment period (12 weeks) during these pollen seasons, except for no-symptom patients who were sensitized to orchardgrass, mugwort, or ragweed. Similarly, patients who did not respond to treatment with the usual dose of antihistamines for AR were excluded.

Patients with PAR could continue the bilastine treatment if they met the following transition criteria: the patient elected continuous treatment with bilastine, the investigators decided to continue the treatment based on improvement of nasal symptoms during the 12-week treatment (assessment of changes in TNSS at 12 weeks from baseline), and they lacked safety concerns.

2.2. Study design

This open-label, single-arm, phase III study evaluated the safety and efficacy of long-term treatment with bilastine (20 mg, once daily) in patients with SAR or PAR. This study was composed of three periods: observation, treatment (12 weeks; SAR and PAR), and continuous treatment (40 weeks; PAR only). Eligible patients were pre-registered, and then participated in an observational period for 8 days (up to 21 days) to assess their baseline AR symptoms. Patients with SAR or PAR who met the registration criteria and did not violate the exclusion criteria were registered and received bilastine 20 mg once daily in the morning, 1 h before or 2 h after breakfast, for 12 weeks (treatment period). Patients with PAR who met the transition criteria could continue the bilastine treatment for an additional 40 weeks (continuous treatment period; 52 weeks in total).

Safety and tolerability were the primary desired outcomes of this study, based on assessment of the incidence and severity of adverse events (AEs), vital signs, laboratory tests (clinical chemistry, hematology, and urinalysis), and a 12-lead electrocardiogram (ECG). AEs were monitored during the study period. The secondary endpoint was to evaluate changes in efficacy variables from baseline: TNSS (sum of rhinorrhea, sneezing, nasal congestion, and itching), total ocular symptom score (TOSS; sum of eye itching and lacrimation), total symptom score (TSS; sum of nasal and ocular symptom scores), individual nasal and ocular symptom scores, QOL score determined using the Japanese Allergic Rhinitis QOL Standard Questionnaire No. 1 [2], and degree of patient satisfaction with the treatment. The patients were instructed to record their symptom scores (individual nasal and ocular symptoms) in a patient diary daily during the observation and treatment periods, as described in a previous report [9]. Briefly, rhinorrhea, sneezing, nasal congestion, eye itching, and lacrimation were assessed on a five-point scale, and nasal itching was assessed on a four-point scale. The baseline and assessment point values for TNSS, TOSS, TSS, and for each

symptom were determined using the average score during the 4 consecutive days prior to the first day of bilastine administration and the 7 consecutive days before each patient visit, respectively.

This study 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-142622).

2.3. Statistical analyses

Safety analyses were performed using a safety population (SP) of patients, who received at least one dose of bilastine. The AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1, and were summarized using descriptive statistics. The efficacy analyses were performed using a long-term efficacy analysis population of patients who received at least one dose of bilastine, completed the study without violating the patient inclusion or exclusion criteria protocols, and underwent at least 1 day of TNSS assessment. All statistical analyses were performed using the statistical analysis software (SAS) version 9.2 (SAS Institute, Cary, NC). All reported *P*-values were two-sided, and *P* < 0.05 was considered statistically significant.

3. Results

3.1. Demographics

We enrolled 92 patients with SAR, and 80 patients with PAR; a total of 58 patients with SAR, and 64 patients with PAR were ultimately registered in this study.

One patient (1.7%) with SAR withdrew from the study during the treatment period (for personal reasons). Fifty-six patients (96.6%) completed the study before the end of the 12-week treatment period because the investigators judged that they did not require further bilastine treatment, based on their symptoms after the JC and cypress pollen seasons.

Two patients (3.1%) with PAR were withdrawn from the study during the treatment period (withdrawal of patient consent, lack of efficacy as judged by the investigator). A total of 55 patients (85.9%) were transitioned to the continuous treatment period, and 7 patients (10.9%) ended their participation at the end of the treatment period (12 weeks) because they did not meet the transition criteria.

The demographic and baseline characteristics of the safety population (SP) are summarized in Table 1. Median exposure to bilastine for patients with SAR or PAR was 70 or 363 days, respectively (Table 2).

3.2. Safety during the 12-week treatment for SAR

AEs were reported by 17.2% (10/58) of patients during the 12 weeks of treatment with bilastine for SAR (Table 3). All of

Table 1

Patient demographics and characteristics at baseline in the safety population (SP).

Variable	SAR (n = 58)	PAR (n = 64)
Gender		
Males [n (%)]	22 (37.9)	24 (37.5)
Females [n (%)]	36 (62.1)	40 (62.5)
Age (years) [mean ± SD]	38.5 ± 9.7	41.5 ± 10.2
BMI (kg/m ²) [mean ± SD]	22.41 ± 2.91	22.13 ± 3.85
Duration of AR (months) [mean ± SD]	232.2 ± 111.2	303.1 ± 116.9
TNSS [mean ± SD]	10.06 ± 1.35	7.76 ± 1.70
TOSS [mean ± SD]	4.62 ± 1.68	2.86 ± 1.32
TSS [mean ± SD]	14.67 ± 2.56	10.62 ± 2.38
Classification of the severity of allergic rhinitis symptoms [N (%)]		
Most severe	6 (10.3)	2 (3.1)
Severe	31 (53.4)	12 (18.8)
Moderate	21 (36.2)	41 (64.1)
Mild	0 (0.0)	9 (14.1)
No symptoms	0 (0.0)	0 (0.0)

AR, allergic rhinitis; BMI, body mass index; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SD, standard deviation; TNSS, total nasal symptom score; TOSS, total ocular symptom score; TSS, total symptom score.

the AEs were mild or moderate (8.6% of each) in intensity, and unrelated to the treatment. The following AEs were reported by $\geq 2\%$ of patients: nasopharyngitis (8.6%) and upper respiratory tract infection (3.4%). The incidence of these AEs did not increase during treatment in a duration-dependent manner (Supplemental Table 1). The AEs were categorized using the System Organ Class of nervous system disorders, were not reported during the 12-week treatment with bilastine. There were no serious AEs or deaths, and no patients withdrew from the study because of AEs. No clinically meaningful changes were observed in vital signs or laboratory variables during the study. No clinically relevant abnormalities were observed on the 12-lead ECG.

3.3. Safety during the 52-week treatment for PAR

The AEs reported by $\geq 2\%$ of patients over the 52-week treatment for PAR are summarized in Table 4. AEs were reported by 31.3% (20/64) of patients or 73.4% (47/64) of

Table 2

Summary of the extent of exposure to bilastine in the safety population (SP).

	SAR (n = 58)	PAR (n = 64)
Total administration period (weeks) [n (%)]		
≤ 2	0 (0.0)	0 (0.0)
$>2, \leq 4$	0 (0.0)	1 (1.6)
$>4, \leq 8$	2 (3.4)	0 (0.0)
$>8, \leq 12$	56 (96.6)	6 (9.4)
$>12, \leq 24$	–	3 (4.7)
$>24, \leq 36$	–	1 (1.6)
$>36, \leq 48$	–	0 (0.0)
$>48, \leq 52$	–	50 (78.1)
>52	–	3 (4.7)
Exposure (days)		
Mean ± SD	68.4 ± 4.1	315.9 ± 102.6
Median	70.0	363.0
Min–Max	56–78	16–371

PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SD, standard deviation.

Table 3Adverse events (AEs) reported by $\geq 2\%$ of patients, and adverse drug reactions (ADRs) over 12-week treatment period in patients with seasonal allergic rhinitis in safety population (SP).

	n (%) n = 58
Patients reporting ≥ 1 AE	10 (17.2)
Incidence of AE ^a $\geq 2\%$	
Nasopharyngitis	5 (8.6)
Upper respiratory tract infection	2 (3.4)
Withdrawals due to AEs	0 (0.0)
Serious AEs	0 (0.0)
Patients reporting ≥ 1 ADR	0 (0.0)

^a MedDRA (ver. 17.1) Preferred Term.

patients during the 12-week or 52-week treatment periods, respectively. Most of the AEs were mild (57.8%) or moderate (46.9%) in intensity, but one patient reported adenomyosis of the uterus with severe AE (1.6%), which occurred at 315 days after the beginning of administration. The investigator considered this AE to have been caused by a natural progression, because it had been present before the bilastine treatment, and was deemed unrelated to the bilastine treatment. The AEs reported by $\geq 5\%$ of patients were seasonal allergy (51.6%), nasopharyngitis (20.3%), and increased blood triglycerides (6.3%). Several patients who have been complicated with JC pollinosis before the study enrollment reported experiencing JC pollinosis after the transition to the continuous treatment period, which explains the high incidence of seasonal allergies. No patient showed new development of pollinosis during the pollen season. The incidence of AEs possibly or probably related to treatment as assessed by the investigators (adverse drug reactions: ADRs) was 6.3% (4/64 patients), with the following breakdown: thirst, 3.1% (2/64 patients), and upper abdominal pain and headache, each at 1.6% (1/64 patients). All of the ADRs occurred within the 2-week treatment period, and were mild in severity. The incidence of AEs/ADRs did not increase during the treatment period in a duration-dependent manner (Supplementary Table 2). The AEs were categorized using the System Organ Class of nervous system disorders; headache was reported by 4.7% (3/64) of patients during the 52-week period, and by 2 patients during the 12-week treatment period. There were no deaths, and no patients withdrew from the study because of AEs. No clinically meaningful changes were observed in vital signs or laboratory variables during the study. No clinically relevant abnormalities were observed on the 12-lead ECG.

3.4. Efficacy in SAR

The study in patients with SAR was conducted at a single site in Tokyo. Fig. 1 shows the changes in TNSS (A), TOSS (B), and TSS (C) from baseline over the 8 weeks of treatment in patients with SAR, and pollen counts during the 2015 cedar pollen season in Tokyo. We planned to evaluate the efficacy at 2, 4, 8, and 12 weeks after bilastine treatment. However, 56 (96.6%) patients completed the study before the end of the 12 weeks because the investigators determined that they did not

Table 4

Adverse events (AEs) reported by $\geq 2\%$ of patients, and adverse drug reactions (ADRs) over 52-week treatment period in patients with perennial allergic rhinitis in safety population (SP).

	n (%) n = 64
Patients reporting ≥ 1 AE	47 (73.4)
Incidence of AE ^a $\geq 2\%$	
Seasonal allergy	33 (51.6)
Nasopharyngitis	13 (20.3)
Blood triglycerides increased	4 (6.3)
Headache	3 (4.7)
Upper abdominal pain	2 (3.1)
Thirst	2 (3.1)
Gastroenteritis	2 (3.1)
Influenza	2 (3.1)
Traffic accident	2 (3.1)
White blood cell increased	2 (3.1)
Urinary protein positive	2 (3.1)
Back pain	2 (3.1)
Allergic bronchitis	2 (3.1)
Eczema	2 (3.1)
Withdrawals due to AEs	0 (0.0)
Serious AEs	1 (1.6)
Patients reporting ≥ 1 ADR ^a	4 (6.3)
Thirst	2 (3.1)
Upper abdominal pain	1 (1.6)
Headache	1 (1.6)

^a MedDRA (ver. 17.1) Preferred Term.

need further bilastine treatment, based on assessment of patient symptoms. In addition, it was shown after study completion that the efficacy assessment at 8 weeks was performed after the end of the pollen season, based on data on JC and cypress pollen dispersal in 2015 (Fig. 1). Therefore, we concluded that the most appropriate point for efficacy evaluation was the 4-week point. We found that bilastine significantly decreased TNSS, TOSS, and TSS from 2 to 4 weeks after baseline ($P < 0.01$). Improvements in TNSS, TOSS, and TSS following bilastine treatment were also observed early in treatment (days 1–3). Moreover, nasal and ocular symptoms were significantly decreased at 2–4 weeks (data not shown). QOL scores, both the sum and individual domain components (outdoor activities, sleeping, physical activities, and mental life) were also improved at 4 weeks, as shown in Fig. 3A. The proportion of patients who were satisfied or very satisfied at 2 weeks was 53.4% (31/58 patients) (Fig. 4A).

3.5. Efficacy in PAR

The study in patients with PAR was conducted at a single site in Osaka. Fig. 2 shows changes in TNSS (A), TOSS (B), and TSS (C) from baseline over the 52 weeks of treatment in patients with PAR, and pollen counts during the 2015 cedar pollen season in Osaka. TNSS and TSS scores significantly decreased from baseline over the 52 weeks of treatment with bilastine ($P < 0.01$). TOSS was also significantly improved by bilastine during the 52-week period, except at 20 and 24 weeks. Patient visits to investigate efficacy at 24–32 weeks corresponded to the 2015 JC and cypress pollen season (Fig. 2).

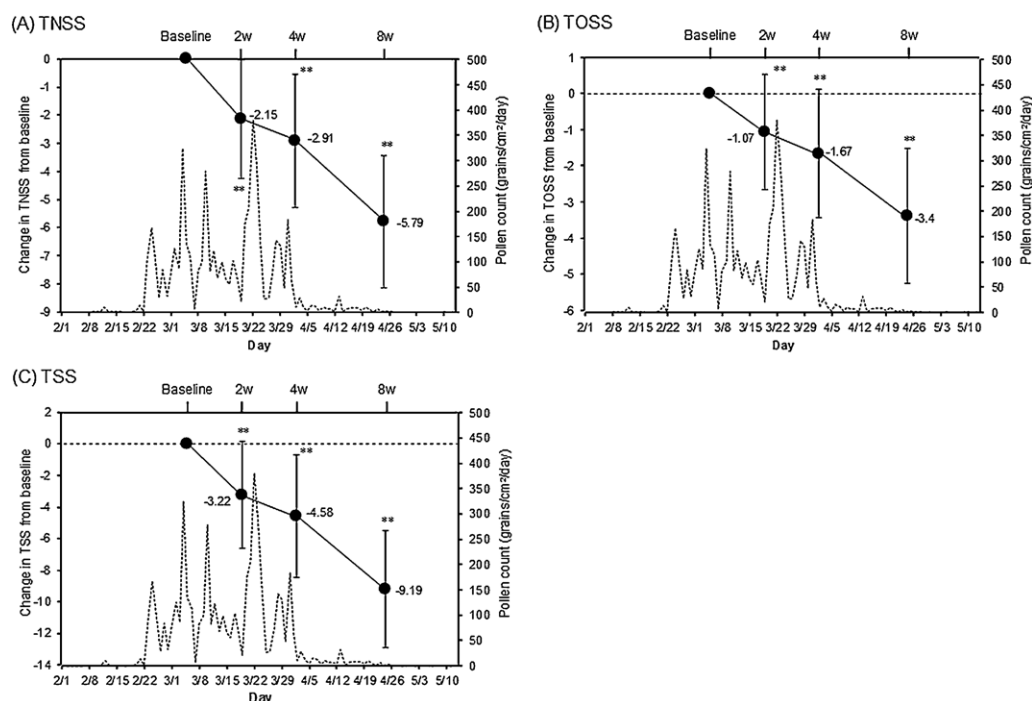


Fig. 1. Change in total nasal symptom score (TNSS: A), total ocular symptom score (TOSS: B), and total symptom score (TSS: C) from baseline over 8 weeks (w) in SAR, and pollen counts (Japanese cedar + cypress pollen) during the 2015 cedar pollen scattering season in Tokyo. Each value represents mean $\pm$ SD (number of patients; baseline, 2 w, 4 w: $n = 58$, 8 w: $n = 57$). Pollen counts (dashed line) are indicated as the mean of 5 observation points (Chiyoda-ku, Katsushika-ku, Suginami-ku, Kita-ku, and Ohta-ku) in Tokyo, obtained from the Tokyo Metropolitan Institute of Public Health (Tokyo, Japan). ** $P < 0.01$ vs. baseline (paired t -test), analytical object: the long-term efficacy analysis population. w; weeks.

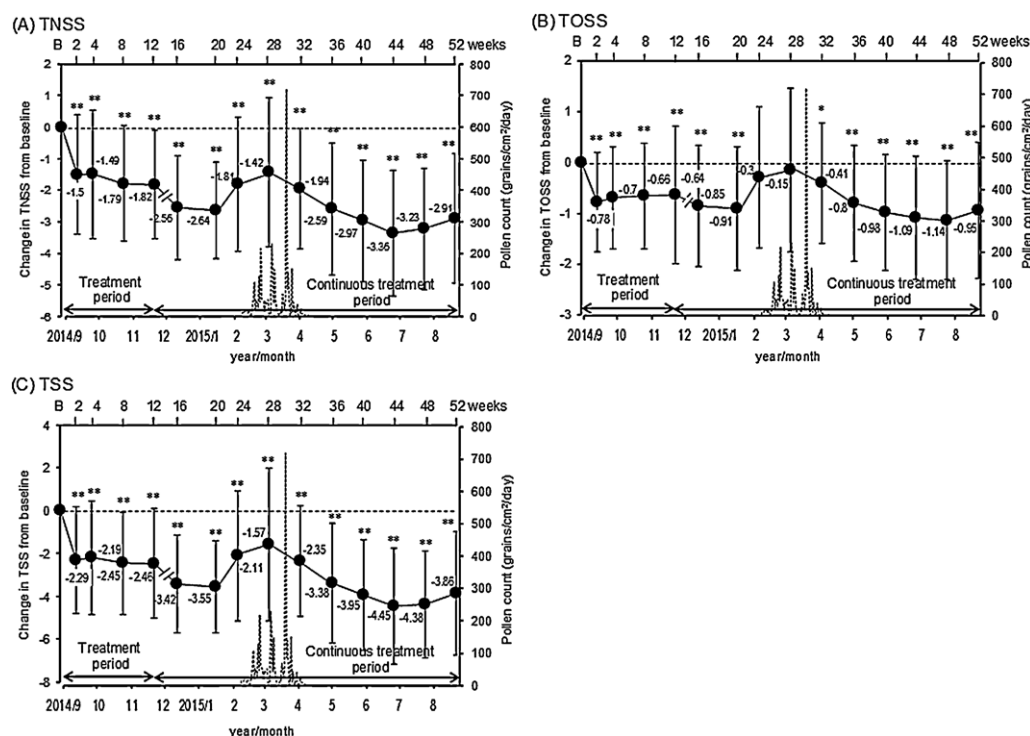


Fig. 2. Change in total nasal symptom score (TNSS: A), total ocular symptom score (TOSS: B), and total symptom score (TSS: C) from baseline during the 52 weeks (w) in PAR, and pollen counts (Japanese cedar + cypress pollen) during the 2015 cedar pollen scattering season in Osaka. Each value represents mean $\pm$ SD (number of patients; baseline: $n = 64$, 2 w: $n = 63$, 4 w: $n = 62$, 16 w: $n = 55$, 24 w: $n = 54$, 28 w: $n = 53$, 32 w: $n = 52$, 48 w: $n = 52$). Pollen count (dashed-line) data were obtained from the Ibaraki Public Health Center (Osaka, Japan). B: baseline. * $P < 0.05$, ** $P < 0.01$ vs. baseline (paired t -test), analytical object: the long-term efficacy analysis population.

Thus, TNSS, TOSS, and TSS gradually decreased from baseline to 20 weeks, and showed a partial increase at 24–32 weeks, then gradually decreased until 52 weeks (Fig. 2). A total of 33 patients reported seasonal allergies (pollinosis) during the pollen season. Therefore, the increase in TNSS, TOSS, and TSS at 24–32 weeks was due to JC pollinosis caused by onset of the pollen season. Comparison of patients with or without JC pollinosis showed that TNSS did not increase in patients without JC pollinosis at 24–32 weeks, but patients with JC pollinosis showed an increase in TNSS at 24–32 weeks (Supplemental Fig. 1). Improvement of TNSS, TOSS, and TSS by bilastine was also observed in early treatment (days 1–3). Moreover, significantly decreased nasal or ocular symptoms from baseline were observed over the 52 weeks, similar to TNSS and TOSS, respectively (data not shown). QOL score, both the sum and each domain component (daily life, sleeping, and physical activities) improved after the end of the treatment period (12 weeks) as shown in Fig. 3B, and the improvement was maintained during the 52-week treatment period (data not shown). The proportion of patients who were satisfied or very satisfied at 2, 12, 24, 36, and 52 weeks was 27.0% (17/63 patients), 35.5% (22/62), 48.1% (26/54), 52.8% (28/53), and 61.5% (32/52), respectively (Fig. 4B).

4. Discussion

The aim of this study was to determine the long-term safety and efficacy of bilastine treatment for Japanese patients with SAR and PAR.

With respect to safety, there did not appear to be any cause for concern following long-term administration of bilastine. AEs were reported by 17.2% (10/58) of patients with SAR, and by 31.3% (20/64) of patients with PAR during the 12-week treatment period (total: 24.6% [30/122]). ADRs were reported by 6.3% (4/64) of patients with PAR, but none were reported by patients with SAR in the 12-week treatment period. All ADRs were mild in severity. There were no serious AEs or deaths, and no patients withdrew from the study because of AEs during the 12-week treatment period. Moreover, AEs and ADRs were reported by 73.4% (47/64) and 6.3% (4/64) of patients with PAR during the 52-week treatment with bilastine. The incidence of AEs was higher in the 52-week treatment period than in the 12-week treatment period. This was due to the occurrence of pollinosis in patients who experienced JC pollinosis during the pollen season after the transition to the continuous treatment period. Moreover, all ADRs occurred during the 12-week treatment period, but none occurred during the continuous treatment period. The AEs were categorized using the System Organ Class of nervous system disorders; headache was reported by 4.7% (3/64), and somnolence, which is a classic effect of antihistamines, was not reported during the study period. A serious AE was reported by one patient with PAR, but was considered unrelated to the bilastine treatment. There were no deaths, and no patients withdrew from the study because of AEs during the 52-week treatment period. Comparison of the present study and an overseas study that reported the long-term safety of bilastine during 1 year in patients with PAR [10] showed that the incidence of ADRs was

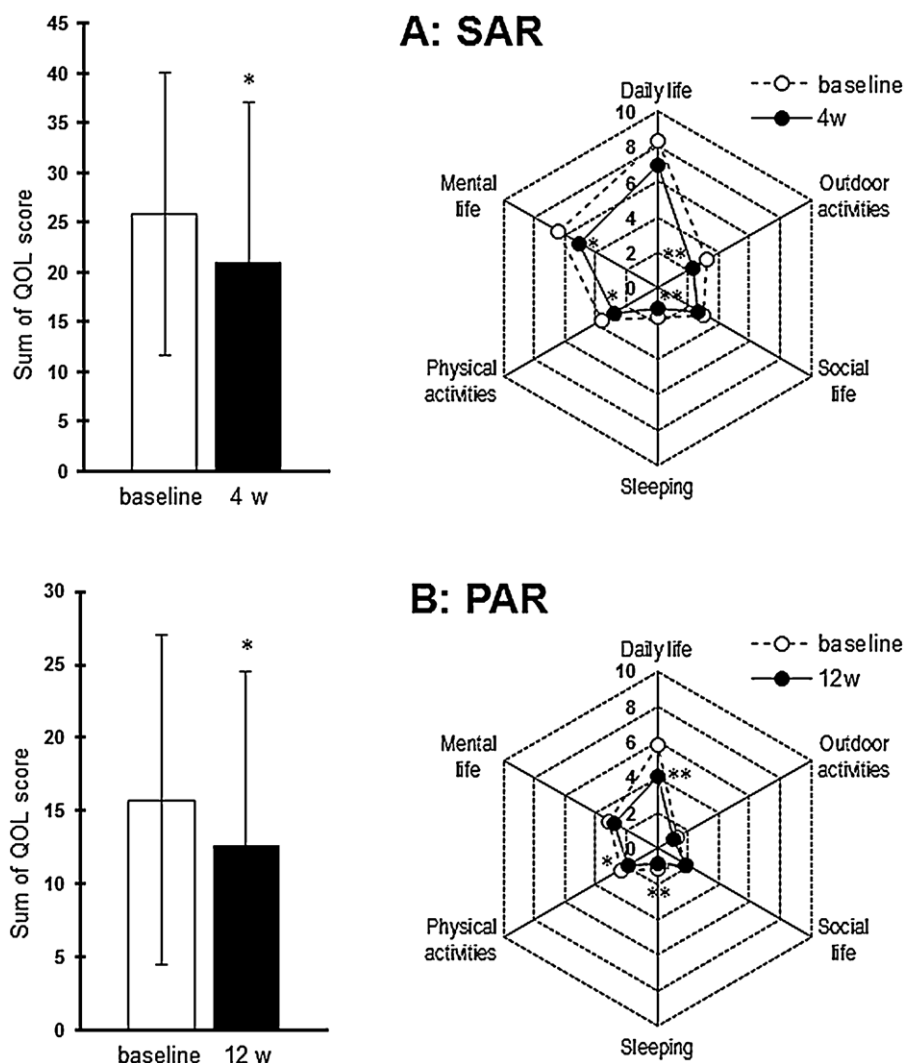


Fig. 3. Total and domain components (daily activities, outdoor activities, social life, sleeping, physical activities, and mental life) of QOL scores at baseline, after 4 weeks (w) of treatment for SAR (A), and after 12 w of treatment for PAR (B). Total QOL represents mean $\pm$ SD (number of patients; baseline and 4 w for SAR: $n = 64$, baseline: $n = 64$, 12 w: $n = 62$ for PAR). Each domain component indicates the mean value. * $P < 0.05$, ** $P < 0.01$ vs. baseline (paired t -test), analytical object: the long-term efficacy analysis population. QOL, quality of life.

lower during the 52 weeks of the present study than in the overseas study, and no particular ADRs were observed in Japanese patients with PAR. No clinically meaningful changes were observed in vital signs or laboratory variables during the

study, and no clinically relevant abnormalities were observed on the 12-lead ECG. These results clearly demonstrate that bilastine was safe and well tolerated in the long-term treatment for AR.

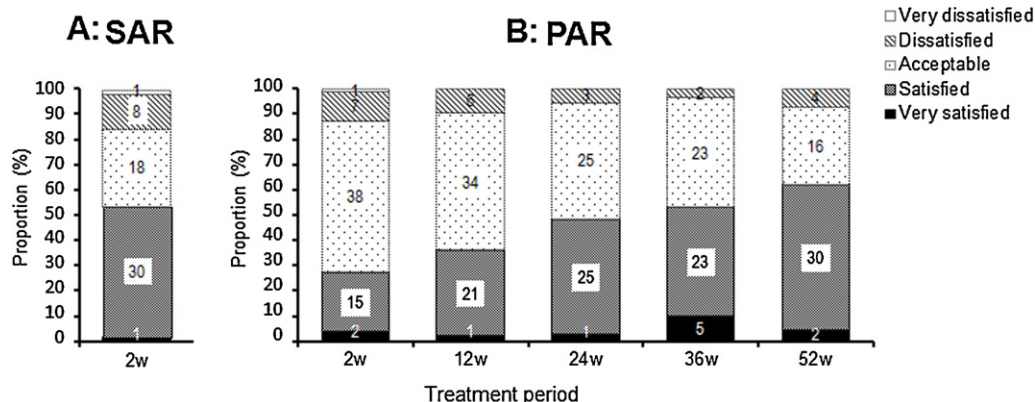


Fig. 4. Patient's global treatment satisfaction at 2 weeks (w) for SAR (A), and over the 52 w for PAR (B). Analytical object: the long-term efficacy analysis population.

Compared with baseline, bilastine significantly decreased TNSS, TOSS, and TSS from days 1–3 to 4 weeks, and improvement of QOL was also observed at 4 weeks in patients with SAR. Similarly, prolonged treatment with bilastine resulted in maintenance of a significant reduction in TNSS, TOSS, and TSS from baseline in patients with PAR during the 52-week treatment period, in spite of the partial increase in TNSS, TOSS, and TSS observed at 24–32 weeks due to JC pollinosis in some patients. Improvement of QOL was also observed during the 52-week treatment, and the proportion of patients satisfied with the treatment increased in a duration-dependent manner. During the 52-week period, a total of 7 patients (10.9%) with PAR discontinued treatment due to lack of efficacy. These results suggested that bilastine was effective for patients with SAR and PAR, and the improvement was maintained for the duration of the study with no loss of drug efficacy.

In conclusion, bilastine (20 mg, once daily) was safe, well tolerated, and effective in long-term treatment for Japanese patients with AR.

Conflicts of interest

K. Okubo received adviser fees from TAIHO Pharmaceutical Co. M. Togawa and A. Saito are employees of TAIHO Pharmaceutical Co. M. Gotoh and Y. Ohashi have no conflicts of interest regarding the content of this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.anl.2016.07.021>.

References

- [1] Pawankar R, Canonica GW, Holgate ST, Lockey RF. WAO white book on allergy 2013 update. Milwaukee, WI: World Allergy Organization; 2013. p. 27–30.
- [2] Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H, et al. Japanese guideline for allergic rhinitis 2014. *Allergol Int* 2014;63: 357–75.
- [3] Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152:S1–43.
- [4] Fujieda S, Kurono Y, Okubo K, Ichimura K, Enomoto T, Kawauchi H, et al. Examination, diagnosis and classification for Japanese allergic rhinitis: Japanese guideline. *Auris Nasus Larynx* 2012;39:553–6.
- [5] Lehman JM, Blaiss MS. Selecting the oral antihistamine for patients with allergic rhinitis. *Drugs* 2006;66:2309–19.
- [6] Walsh GM. Emerging safety issues regarding long-term usage of H₁-receptor antagonists. *Expert Opin Drug Saf* 2002;1:225–35.
- [7] Yanai K, Rogala B, Chugh K, Paraskakis E, Pampura AN, Boev R. Safety considerations in the management of allergic diseases: focus on antihistamines. *Curr Med Res Opin* 2012;28:623–42.
- [8] Ilaxten 20 mg tablets. Bilastine 20 mg. Summary of product characteristics. Available from: http://www.mhra.gov.uk/spc-pil/?prodName=ILAXTEN20MG_TABLETS&subsName=&pageID=ThirdLevel&searchTerm=bilastine#retainDisplay [accessed 27.11.15].
- [9] Okubo K, Gotoh M, Asako M, Nomura Y, Togawa M, Saito A, 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. *Allergol Int* 2016. Available online 14 July 2016: <http://dx.doi.org/10.1016/j.alit.2016.05.014>.
- [10] ICH Steering Committee. ICH Harmonised Tripartite Guideline: the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions; 1994 October.
- [11] Sastre J, Mullol J, Valero A, Valiente R. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo in the treatment of perennial allergic rhinitis. *Curr Med Res Opin* 2012;28:121–30.

Supplementary Table 1. Adverse events (AEs) reported by $\geq 2\%$ of patients, and adverse drug reactions (ADRs) by time of onset during the 12-week treatment period in patients with seasonal allergic rhinitis in the safety population (SP)

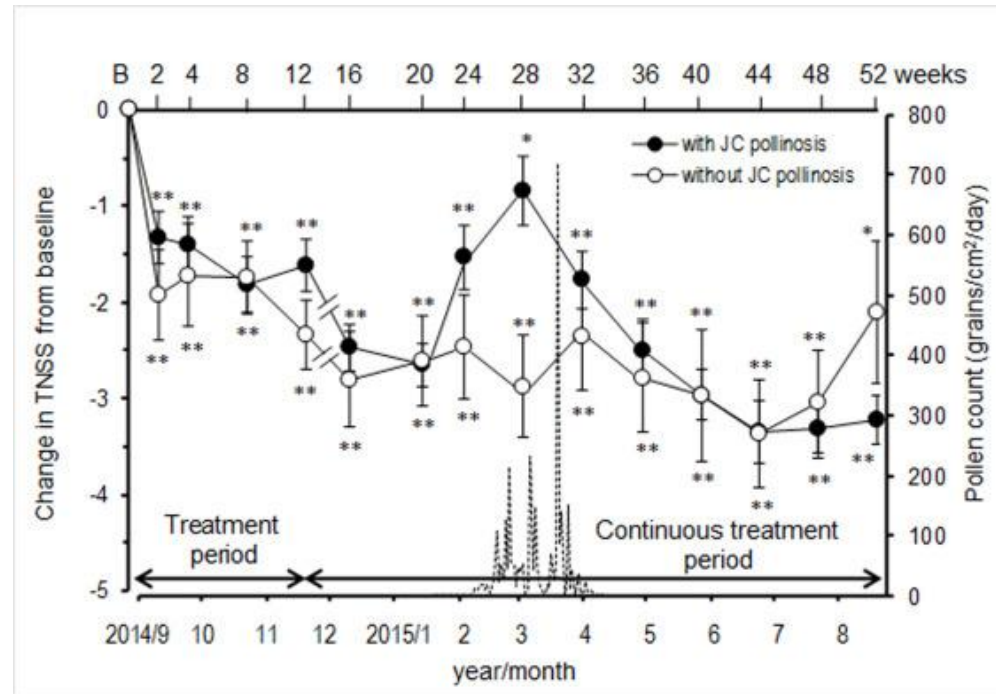
Time of onset (weeks)	Total	≤ 2	$>2, \leq 4$	$>4, \leq 8$	$>8, \leq 12$
Number of patients at start of time interval	n = 58	n = 58	n = 58	n = 58	n = 56
Patients reporting ≥ 1 AE [n (%)]	10 (17.2)	2 (3.4)	4 (6.9)	3 (5.2)	1 (1.8)
Incidence of AE [†] $\geq 2\%$					
Nasopharyngitis	5 (8.6)	1 (1.7)	0 (0.0)	3 (5.2)	1 (1.8)
Upper respiratory tract infection	2 (3.4)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)
Withdrawals due to AEs	0 (0.0)	-	-	-	-
Serious AEs	0 (0.0)	-	-	-	-
Patients reporting ≥ 1 ADR [n (%)]	0 (0.0)	-	-	-	-

[†]MedDRA (ver. 17.1) Preferred Term

Supplementary Table 2. Adverse events (AEs) reported by $\geq 2\%$ of patients, and adverse drug reactions (ADRs) by time of onset during the 52-week treatment period in patients with perennial allergic rhinitis in the safety population (SP)

Time of onset (weeks)	Total	≤ 12	$>12, \leq 24$	$>4, \leq 36$	$>36, \leq 48$	>48
Number of patients at start of time interval	n = 64	n = 64	n = 57	n = 54	n = 53	n = 53
Patients reporting ≥ 1 AE [n (%)]	47 (73.4)	20 (31.3)	35 (61.4)	15 (27.8)	9 (17.0)	6 (11.3)
Incidence of AE [†] $\geq 2\%$						
Seasonal allergy	33 (51.6)	0 (0.0)	28 (49.1)	5 (9.3)	0 (0.0)	0 (0.0)
Nasopharyngitis	13 (20.3)	5 (7.8)	3 (5.3)	3 (5.6)	1 (1.9)	1 (1.9)
Blood triglycerides increased	4 (6.3)	2 (3.1)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)
Headache	3 (4.7)	2 (3.1)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Upper abdominal pain	2 (3.1)	1 (1.6)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Thirst	2 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	2 (3.1)	1 (1.6)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Influenza	2 (3.1)	0 (0.0)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Traffic accident	2 (3.1)	1 (1.6)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
White blood cell increased	2 (3.1)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Urinary protein positive	2 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)
Allergic bronchitis	2 (3.1)	1 (1.6)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Eczema	2 (3.1)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Withdrawals due to AEs	0 (0.0)	-	-	-	-	-
Serious AEs	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Patients reporting ≥ 1 ADR [†] [n (%)]	4 (6.3)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thirst	2 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper abdominal pain	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[†]MedDRA (ver. 17.1) Preferred Term



Supplementary Fig. S1. Change in total nasal symptom score from baseline over the 52 weeks (w) in PAR patients who presented with or without Japanese cedar (JC) pollinosis, and pollen counts (Japanese cedar + cypress pollen) during the 2015 cedar pollen scatte...

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