JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13644
Journal of Dermatology 2017; **44**: 375–385

ORIGINAL ARTICLE

One-year safety and efficacy study of bilastine treatment in Japanese patients with chronic spontaneous urticaria or pruritus associated with skin diseases

Akiko YAGAMI,[1] Masutaka FURUE,[2] Michinori TOGAWA,[3] Akihiro SAITO,[3] Michihiro HIDE[4]

[1]*Department of Dermatology, School of Medicine, Fujita Health University, Aichi,* [2]*Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka,* [3]*Clinical Development Division, TAIHO Pharmaceutical, Tokyo,* [4]*Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*

ABSTRACT

A number of second-generation non-sedating antihistamines are used in clinical practices over the world. However, long-term safety and efficacy have not been proved high level evidence based medicine. We have performed an open-label, multicenter, phase III study to evaluate the long-term safety and efficacy of bilastine, a novel non-sedating H_1-antihistamine for patients with chronic spontaneous urticaria (CSU) or pruritus associated with skin diseases (trial registration no. JapicCTI-142528). Patients aged 18–74 years were treated with bilastine 20 mg once daily for up to 52 weeks. Safety and tolerability were assessed on the basis of adverse events (AE), bilastine-related AE, laboratory tests and vital signs. Efficacy was assessed based on rash score, itch score, overall improvement and quality of life. One hundred and ninety-eight patients enrolled, 122 of whom (61.6%) completed the 52-week treatment period. AE were reported in 64.5% and bilastine-related AE in 2.5% of patients throughout the 52-week treatment period. All AE were mild to moderate in severity. AE associated with the nervous system occurred in 10 patients (5.1%) including seven patients (3.6%) with headache. Somnolence reported in two of these patients (1.0%) was related to bilastine. All efficacy variables improved during treatment with bilastine. In conclusion, long-term treatment with bilastine 20 mg once daily for 52 weeks is safe and well tolerated in Japanese patients with CSU or pruritus associated with skin diseases. Bilastine improved disease symptoms of both conditions early in treatment, and the efficacy was maintained throughout the treatment.

Key words: **bilastine, chronic spontaneous urticaria, eczema/dermatitis, H_1-antihistamine, pruritus.**

INTRODUCTION

Pruritus is an unpleasant sensation in the skin that causes an intense desire to scratch and highly influences the quality of life (QOL).[1–3] It is the most frequent symptom in dermatology and can be distinguished as acute or chronic pruritus (CP), with the latter defined by the International Forum of Itch as pruritus lasting 6 weeks or more.[4]

Multiple factors contribute to the induction and exacerbation of pruritus. The most important factors in the elicitation of itch are resident skin cells, which can release mediators that directly induce itch by binding to pruriceptors or indirectly by releasing products that activate other cells to release pruritogenic substances.[5] Among them, histamine has been the most thoroughly studied pruritogen for decades. Histamine binds to H_1-receptors expressed on sensory nerve fibers and endothelial vessel walls. i.d. injection of histamine provokes vasodilation with wheal and flare accompanied by pruritus. H_1-antihistamines are the only available antipruritic therapy for various types of pruritus and are very effective when the itch sensation is mediated by histamine, like in urticaria. Clinical aspects for the treatment of urticaria with H_1-antihistamines in the Japanese guideline for urticaria[6] are similar to those in the guidelines used in Europe[7] or the USA.[8] However, while the European guideline on CP states that H_1-antihistamines have limited efficacy at the licensed dose in any type of CP,[9] the Japanese guideline for management of atopic dermatitis[10] states that the Japanese Dermatological Association recommends second-generation H_1-antihistamines for suppressing pruritus and preventing exacerbation due to scratching as an adjuvant therapy for topical treatments, as well as for chronic prurigo or cutaneous pruritus (described in Japanese only). Accordingly, most second-generation H_1-antihistamines have been authorized for the treatment of urticaria and pruritus associated with skin diseases (e.g. eczema/dermatitis, cutaneous pruritus) in Japan.

Correspondence: Akiko Yagami, M.D., Ph.D., Department of Dermatology, Fujita Health University, School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. Email: ayagami@fujita-hu.ac.jp
Received 8 August 2016; accepted 2 September 2016.

Bilastine is a non-sedating second-generation H_1-antihistamine. As of March 2015, bilastine has been approved for the therapeutic use for urticaria and allergic rhinitis (AR) with a recommended dose of 20 mg once daily in patients older than 12 years in 90 countries, but not in Japan. A clinical pharmacological study using positron emission tomography demonstrated that a single p.o. dose of bilastine 20 mg did not occupy the H_1-receptors in the brains.[11] Furthermore, bilastine at therapeutic and supratherapeutic doses (20 and 100 mg once daily, respectively) did not induce any clinically significant changes on QT interval corrected for heart rate prolongation in electrocardiogram,[12] and bilastine requires no dose adjustment in patients with renal dysfunction.[13]

In randomized double-blind studies in Japan, the efficacy of 2-week treatment with bilastine 20 mg once daily was superior to that of a placebo in Japanese patients with chronic spontaneous urticaria (CSU)[14] or perennial AR.[15] However, no clinical study to evaluate the safety and efficacy of long-term administration of bilastine has been conducted in Japanese patients with CSU or AR. Moreover, the efficacy and safety of bilastine 20 mg once daily in patients with pruritus associated with skin diseases has not been fully elucidated. The International Conference on Harmonization E1 requires 12-month treatment data and inclusion of treatment outcomes of at least 100 patients treated for at least 1 year in the safety database for evaluation of novel drugs of which long-term use is expected.[16] However, such a long-term clinical trial has not been performed in Japan. In the present study, we evaluated the long-term (52-week) safety and efficacy of bilastine 20 mg once daily in Japanese patients with CSU or pruritus associated with skin diseases (eczema/dermatitis, prurigo or cutaneous pruritus).

METHODS

Study design and treatment

This was a phase III, open-label, single-arm, multicenter study conducted at 15 clinics in Japan. It involved a 4–14-day run-in period in which patients were screened. Eligible patients were enrolled in a 12-week treatment period. Patients were allowed to move to the continued treatment period (40 weeks) if their symptom scores (total symptom score [TSS] for CSU, itch score for pruritus associated with skin diseases) on week 12 were improved in comparison to the baseline and no severe bilastine-related adverse events (AE) had occurred.

Bilastine (Taiho Pharmaceutical, Tokyo, Japan) 20 mg was administrated once daily in the morning, 1 h or more before or 2 h or more after breakfast, starting from day 1 after enrollment. Follow-up visits were scheduled in weeks 2, 4, 8 and 12 in the 12-week treatment period, and every 4 weeks in the continued treatment period.

Patients

Male and female patients, aged 18–74 years, were screened if they were diagnosed with CSU characterized by recurrent idiopathic rash occurring for at least 4 weeks prior to consent acquisition or with pruritus associated with the following skin diseases: eczema/dermatitis (suitable for evaluating itch from eczema, contact dermatitis, atopic dermatitis, nummular eczema, autosensitization dermatitis, pompholyx, asteatotic eczema or lichen simplex chronicus, except patients with hand eczema alone), prurigo (acute, subacute or chronic) and cutaneous pruritus (systemic or local). Patients could be enrolled in the 12-week treatment period if they demonstrated a total itch score of 8 or more (maximum score of 24, as a sum of daytime and nighttime scores) and a total rash (synthetic) score of 5 or more (maximum score of 9) in case of CSU for 3 days immediately prior to enrollment. Patients were required to record symptom scores in a diary for the last 3 days before enrollment and to have more than 80% of symptom scores completed over the run-in period.

The main exclusion criteria were having a dermatological condition that could interfere with the efficacy evaluation (including angioedema, cholinergic urticaria, mechanical urticaria, aspirin-induced urticaria, urticaria associated with vasculitis or collagen disorder, urticaria with known causes, urticaria related to thyroid disorders, urticaria pigmentosa, food-dependent exercise-induced anaphylaxis, Schnitzler syndrome, cryopyrin-associated periodic syndrome, psoriasis or ichthyosis); a history of hypersensitivity to antihistamine; clinically significant hepatic, renal, cardiac, neurological, hematological, immunological or malignant diseases; receiving ultraviolet light therapy; having received antihistamines, antiallergy drugs, non-steroidal anti-inflammatory drugs, neurotropin, antiplasmin drugs, glycyrrhizinate, diaminodiphenyl sulfone, psychotropic drugs, antipruritic drugs or other drugs for the target diseases (including Chinese herbal medicines) in the previous 6 days; ebastine in the previous 7 days; corticosteroids (excluding depot formulations), tacrolimus hydrate, immunological drugs or estrogen in the previous 21 days; corticosteroids (depot formulations), P-glycoprotein inhibitors, specific immunotherapy or non-specific modulation therapy in the previous 30 days; and investigational drugs in the 90 days before enrollment. All patients could concomitantly use moisturizing agents that they used before consent acquisition. Topical corticosteroids (weak, medium or strong rank) (Table S1) that had been used for more than 1 week before consent acquisition could be concomitantly used in patients with eczema/dermatitis or prurigo during the study as long as the dose and regimen were not changed. When symptoms transiently worsened, patients could use topical corticosteroids with 1 rank higher potency for 2 weeks in the continued treatment.

Safety assessment

The primary end-points of this study were incidence of AE and bilastine-related AE. The incidence rates of AE and bilastine-related AE were assessed at the onset of the study and monitored over the entire 54-week study. Safety was assessed by means of laboratory tests (biochemistry and hematology), vital signs (blood pressure, body temperature and heart rate), and the incidence and severity of AE. Causal relationships for all AE were categorized by the investigator as probable, possible, unlikely or unrelated. Treatment compliance was assessed through patient diary recording.

Efficacy assessment

The efficacy end-points for CSU were TSS, defined as the sum of the rash (synthetic) and itch (average of daytime and nighttime) scores; the change from baseline in TSS; the score and the change from baseline in rash score (flare, wheal and synthetic) and itch score (daytime, nighttime, and average of daytime and nighttime); overall improvement; and change in QOL. Those for pruritus associated with skin diseases were the score and the change from baseline in itch score (daytime, nighttime and average of daytime and nighttime); overall improvement; change in QOL; and only for the eczema/dermatitis and prurigo groups, the rash score assessed by the investigator and its change from baseline.

The baseline values of each symptom score were the average of the consecutive 4 days prior to day 0. The changes from baseline for each symptom score were calculated as the mean score of the initial 3 days of the treatment period and the mean scores of each 7-day period until follow-up visit at weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52. The baseline scores of QOL and rash score assessed by the investigator were those on day 0.

The patients scored their itch during daytime and nighttime using a 5-point scale (0–4) (Table S2) and patients with CSU additionally scored their rash on a 4-point scale (0–3) (Table S3) throughout the run-in and treatment periods. Patients' assessments were recorded in the patient diary daily until week 4 and, thereafter, 7-day assessments (until follow-up visit) were recorded every 4 weeks.

Overall improvement was evaluated at follow up by the investigator based on the patient diary and clinical observations using a 5-point scale (1–5) (1, markedly improved; 2, moderately improved; 3, mildly improved; 4, no change; 5, exacerbated; Table S4).[17] Similarly, the investigator assessed the change from baseline in rash score in the eczema/dermatitis and prurigo groups according to a 5-point scale (0–4) (0, absent; 1, slight; 2, mild; 3, moderate; 4, severe; Table S5).[10] In addition, the patients assessed their QOL by using the Japanese version of the Dermatology Life Quality Index (DLQI; Finlay and Khan, 1992)[18] at day 0, and weeks 2, 4, 8 and 12 (or at discontinuation) in the 12-week treatment period, and at weeks 24 and 52 (or at discontinuation) in the continued treatment period. The DLQI questionnaire was self-administered and comprised 10 questions that were scored; a higher overall score indicated greater impairment of the patient's QOL.[19] We obtained permission to use the DLQI from Dr A. Y. Finlay and Dr G. K. Khan (Department of Dermatology, Cardiff University School of Medicine) before conducting this study.

Statistical analysis

Safety was analyzed in a safety analysis set comprising the patients who received bilastine at least once. Efficacy was analyzed in the full analysis set comprising patients for whom TSS (in patients with chronic spontaneous urticaria) or itch score (in patients with pruritus associated with skin diseases) was assessed for 1 day or more and who were administrated bilastine at least once and were eligible for enrollment. A paired *t*-test was used to analyze the mean change from baseline for each symptom score. All statistical analyses were performed with SAS software version 9.2 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Ethical approval and clinical trial registration

The study protocol was approved by the institutional review board of each clinic. All participants gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki and the Japanese Good Clinical Practice Guidelines. This study was registered with the Japan Pharmaceutical Information Center (no. JapicCTI-142528).

RESULTS

Study population

Of the 205 patients screened, 198 were enrolled in the study between May and August 2014. One patient discontinued the study before administration, and 197 patients had received bilastine at least once (these patients' data served as the safety analysis set), of whom 56 patients had CSU, 85 eczema/dermatitis, 24 prurigo and 32 cutaneous pruritus (Fig. 1). The full analysis set comprised data from 195 patients after the exclusion of two patients who turned out to be ineligible. Of the 181 patients (91.4%) who completed the 12-week treatment period, 166 (83.8%) took part in the continued treatment, and 122/198 patients (61.6%) completed the 40-week continued treatment. Seventeen patients discontinued because of lack of efficacy or symptom progression in the treatment period and the continued treatment period, of whom 14 patients had eczema/dermatitis, two prurigo and one cutaneous pruritus.

The patient characteristics (safety analysis set) are summarized in Table 1. The mean age was 40.0 years, and 50.3% were male. The main disease was atopic dermatitis (54.1%) in the eczema/dermatitis group. At baseline (the average of the consecutive 4 days prior to day 0), in patients with CSU, TSS (mean ± standard deviation) was 4.46 ± 0.84, itch score 2.44 ± 0.55 and synthetic rash score 2.02 ± 0.41. In the eczema/dermatitis, prurigo and cutaneous pruritus groups, itch score was 2.16 ± 0.54, 1.99 ± 0.50 and 2.39 ± 0.72, respectively. Rash score assessed by the investigator was 2.9 ± 0.6 in the eczema/dermatitis group and 2.6 ± 0.6 in the prurigo group. Total QOL score at baseline was 4.5–8.2.

The compliance rate for bilastine was 98.05 ± 4.33% in the safety analysis set and 97% or more in each disease group. The administration period was 284.3 ± 115.5 days overall, and 319.1 ± 93.6, 262.7 ± 123.3, 266.9 ± 127.5 and 293.7 ± 108.5 days in patients with CSU, eczema/dermatitis, prurigo and cutaneous pruritus, respectively.

Safety

Safety was assessed in 197 patients comprising the safety analysis set over the 12-week and continued treatment periods. The common (≥2%) AE and bilastine-related AE are shown in Table 2. The most common AE were nasopharyngitis (28.4%), contact dermatitis (4.1%), eczema (4.1%), headache (3.6%) and asteatosis (3.6%). AE associated with the nervous

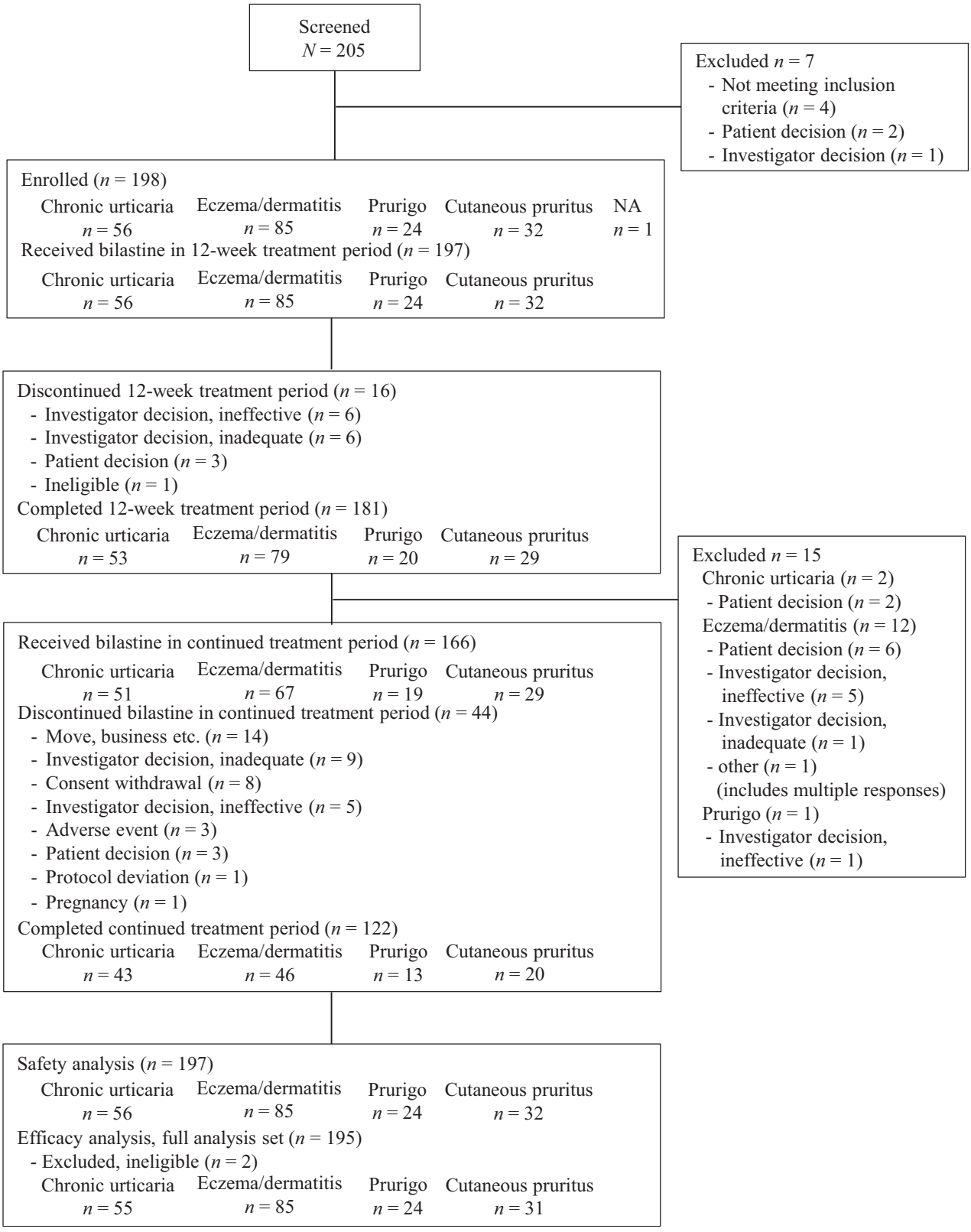

Figure 1. Patient disposition.

Table 1. Patient characteristics

			Pruritus associated with skin diseases		
	Total (n = 197)	Chronic spontaneous urticaria (n = 56)	Eczema/dermatitis (n = 85)	Prurigo (n = 24)	Cutaneous pruritus (n = 32)
Sex (n [%])					
Male	99 (50.3)	22 (39.3)	49 (57.6)	15 (62.5)	13 (40.6)
Female	98 (49.7)	34 (60.7)	36 (42.4)	9 (37.5)	19 (59.4)
Age (years)†	40.0 ± 15.1	42.5 ± 13.8	34.8 ± 14.2	44.9 ± 15.6	45.5 ± 15.7
Weight (kg)†	61.43 ± 12.70	62.91 ± 15.60	61.03 ± 11.84	62.37 ± 11.30	59.18 ± 10.13
Disease in each group of pruritus (n [%])					
Eczema/dermatitis					
Atopic dermatitis	–	–	46 (54.1)	–	–
Chronic eczema	–	–	19 (22.4)	–	–
Acute eczema	–	–	8 (9.4)	–	–
Contact dermatitis	–	–	5 (5.9)	–	–
Autosensitization dermatitis	–	–	3 (3.5)	–	–
Nummular eczema	–	–	2 (2.4)	–	–
Asteatotic dermatitis	–	–	2 (2.4)	–	–
Prurigo					
Chronic prurigo	–	–	–	17 (70.8)	–
Subacute prurigo	–	–	–	5 (20.8)	–
Acute prurigo	–	–	–	2 (8.3)	–
Cutaneous pruritus					
Systemic cutaneous pruritus	–	–	–	–	26 (81.3)
Local cutaneous pruritus	–	–	–	–	6 (18.8)
Baseline score†					
TSS	–	4.46 ± 0.84	–	–	–
Itch score (average of daytime and nighttime)	2.26 ± 0.59	2.44 ± 0.55	2.16 ± 0.54	1.99 ± 0.50	2.39 ± 0.72
Rash score (synthetic)	–	2.02 ± 0.41	–	–	–
Investigator's rash score	–	–	2.9 ± 0.6	2.6 ± 0.6	–
Total QOL score	6.5 ± 4.6	8.2 ± 4.4	6.1 ± 4.5	4.5 ± 3.9	6.0 ± 4.9

†Mean (±standard deviation). Analysis set was safety analysis. TSS, total symptom score; QOL, quality of life.

system occurred in 10 patients (5.1%) including seven patients (3.6%) presenting with headache. Somnolence reported in two of these patients (1.0%) was related to bilastine.

Throughout the 52-week treatment, AE were reported in 64.5% of patients, and most of them were mild to moderate in severity. Bilastine-related AE were reported in four patients (2.0%) in the 12-week treatment and five patients (2.5%) throughout the 52-week treatment period. All bilastine-related AE were mild to moderate.

The common and bilastine-related AE by time of onset are shown in Table 3. In the 12-week treatment, AE were reported in 33.5% of patients, and the incidence rates every 2 weeks were 8.1% in day 1 to week 2, 9.7% in weeks 2–4, 12.1% in weeks 4–8 and 10.8% in weeks 8–12. In the continued treatment, the incidence rate of AE every 12 weeks was 33.7% in weeks 12–24, 31.6% in weeks 24–36, 24.1% in weeks 36–48 and 2.4% in weeks 48–53.

No serious AE occurred during the 12-week treatment period. In the continued treatment period, three patients experienced serious AE (retinal detachment, lumber fracture and cervical epithelial dysplasia), which were not related to bilastine. Three patients discontinued the study owing to AE, namely, asthma, oropharyngeal pain and eczema, all of which were not related to bilastine. There were no deaths in this study.

Efficacy

CSU

Figure 2 shows the changes in TSS throughout the 52-week treatment. TSS significantly improved as compared with the baseline at week 2 and remained at approximately the same level thereafter ($P < 0.001$ vs baseline at each time point, paired t-test). Similar efficacy patterns were observed for rash (data not shown) and itch scores (Fig. 3) ($P < 0.001$ vs baseline at each time point, paired t-test).

Figure 4(a) shows the patients' overall improvement at each visit. As for overall improvement as assessed by the

Table 2. Common (occurring in ≥2% of patients) AE and bilastine-related AE

	Total (n = 197) n (%)	Chronic spontaneous urticaria (n = 56) n (%)	Pruritus associated with skin diseases		
			Eczema/dermatitis (n = 85) n (%)	Prurigo (n = 24) n (%)	Cutaneous pruritus (n = 32) n (%)
Withdrawals due to AE	3 (1.5)	1 (1.8)	0 (0.0)	1 (4.2)	1 (3.1)
Serious AE	3 (1.5)	0 (0.0)	3 (3.5)	0 (0.0)	0 (0.0)
Any AE	127 (64.5)	41 (73.2)	44 (51.8)	15 (62.5)	27 (84.4)
Nasopharyngitis	56 (28.4)	16 (28.6)	23 (27.1)	7 (29.2)	10 (31.3)
Contact dermatitis	8 (4.1)	5 (8.9)	1 (1.2)	1 (4.2)	1 (3.1)
Eczema	8 (4.1)	3 (5.4)	0 (0.0)	2 (8.3)	3 (9.4)
Headache	7 (3.6)	2 (3.6)	3 (3.5)	0 (0.0)	2 (6.3)
Asteatosis	7 (3.6)	0 (0.0)	2 (2.4)	2 (8.3)	3 (9.4)
Folliculitis	5 (2.5)	0 (0.0)	5 (5.9)	0 (0.0)	0 (0.0)
Herpes simplex	5 (2.5)	0 (0.0)	2 (2.4)	0 (0.0)	3 (9.4)
Influenza	5 (2.5)	0 (0.0)	3 (3.5)	1 (4.2)	1 (3.1)
Arthropod sting	5 (2.5)	2 (3.6)	1 (1.2)	0 (0.0)	2 (6.3)
Acne	5 (2.5)	2 (3.6)	1 (1.2)	1 (4.2)	1 (3.1)
Eczema asteatotic	5 (2.5)	2 (3.6)	0 (0.0)	1 (4.2)	2 (6.3)
Dental caries	4 (2.0)	1 (1.8)	2 (2.4)	0 (0.0)	1 (3.1)
Sinusitis	4 (2.0)	3 (5.4)	0 (0.0)	0 (0.0)	1 (3.1)
Ligament sprain	4 (2.0)	0 (0.0)	2 (2.4)	2 (8.3)	0 (0.0)
Excoriation	4 (2.0)	2 (3.6)	1 (1.2)	1 (4.2)	0 (0.0)
Thermal burns	4 (2.0)	2 (3.6)	2 (2.4)	0 (0.0)	0 (0.0)
Skin papilloma	4 (2.0)	3 (5.4)	1 (1.2)	0 (0.0)	0 (0.0)
Hand dermatitis	4 (2.0)	0 (0.0)	1 (1.2)	0 (0.0)	3 (9.4)
Any bilastine-related adverse events	5 (2.5)	2 (3.6)	2 (2.4)	0 (0.0)	1 (3.1)
Aspartate aminotransferase increased	1 (0.5)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
γ-Glutamyltransferase increased	1 (0.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	2 (1.0)	1 (1.8)	1 (1.2)	0 (0.0)	0 (0.0)
Nocturia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)

Analysis set was safety analysis set. AE occurring in 2% or more of patients and all adverse drug reactions are shown. Data included the 12-week treatment and the continued treatment. AE, adverse events.

investigators, markedly improved or moderately improved was observed in 81.8% (45/55) of patients at week 2, 88.7% (47/53) at week 12, 96.0% (48/50) at week 24 and 95.3% (41/43) at week 52.

The results of DLQI assessment (total DLQI score and individual domain scores) are shown in Figure 5(a). The total QOL score was 8.2 ± 4.4 at baseline. The total QOL score significantly improved from baseline as of week 2 and slightly improved thereafter ($P < 0.001$ vs baseline at each time point, paired t-test). Similarly, individual domain scores improved from baseline as of week 2.

Pruritus associated with skin diseases

Figure 3 shows the changes in itch score throughout the 52-week treatment period. Itch score decreased from week 2 as compared with the baseline, and remained significantly improved from baseline throughout the 52-week treatment period in all diseases ($P < 0.001$ vs baseline at each point except for $P = 0.002$ at week 2 in prurigo, paired t-test).

As for overall improvement as assessed by the investigators, markedly improved or moderately improved was observed in 46.4% (39/84) of patients at week 2, 70.5% (55/78) at week 12, 78.7% (48/61) at week 24 and 89.1% (41/46) at week 52 in patients with eczema/dermatitis (Fig. 4b). In the patients with prurigo, it was observed in 56.5% (13/23) of patients at week 2, 70.0% (14/20) at week 12, 88.9% (16/18) at week 24 and 92.3% (12/13) at week 52 (Fig. 4c). In the patients with cutaneous pruritus, it was observed in 66.7% (20/30) of patients at week 2, 89.3% (25/28) at week 12, 95.7% (22/23) at week 24 and 90.0% (18/20) at week 52 (Fig. 4d).

Total QOL score significantly improved from baseline from week 2 onwards for all diseases (except for week 2 in patients with prurigo) (Fig. 5b–d). Similarly, individual domain scores in the eczema/dermatitis and cutaneous pruritus groups improved compared with baseline except for "treatment" in eczema/dermatitis and "personal relationships" in cutaneous pruritus. However, "symptoms/feeling" and "work/school" improved from baseline only in patients with prurigo.

Investigators' rash score was significantly improved from baseline from week 2 onwards in the eczema/dermatitis and prurigo groups ($P < 0.001$ vs baseline at each point except for $P = 0.001$ at week 44 in prurigo, paired t-test) (Fig. 6).

Table 3. Number (%) of common AE and bilastine-related AE by time of onset

Time of onset (weeks) No. of patients at start of time interval	≤12 *n* = 197	>12, ≤24 *n* = 169	>24, ≤36 *n* = 155	>36, ≤48 *n* = 137	>48 *n* = 123	Total *n* = 197
Any AE (*n* [%])	66 (33.5)	57 (33.7)	49 (31.6)	33 (24.1)	3 (2.4)	127 (64.5)
Nasopharyngitis	16 (8.1)	20 (11.8)	15 (9.7)	5 (3.6)	–	56 (28.4)
Contact dermatitis	2 (1.0)	4 (2.4)	1 (0.6)	1 (0.7)	–	8 (4.1)
Eczema	2 (1.0)	2 (1.2)	4 (2.6)	–	–	8 (4.1)
Headache	3 (1.5)	2 (1.2)	1 (0.6)	1 (0.7)	–	7 (3.6)
Asteatosis	1 (0.5)	4 (2.4)	1 (0.6)	1 (0.7)	–	7 (3.6)
Folliculitis	3 (1.5)	1 (0.6)	–	1 (0.7)	–	5 (2.5)
Herpes simplex	1 (0.5)	2 (1.2)	–	2 (1.5)	–	5 (2.5)
Influenza	–	1 (0.6)	4 (2.6)	–	–	5 (2.5)
Arthropod sting	3 (1.5)	–	–	1 (0.7)	1 (0.8)	5 (2.5)
Acne	–	3 (1.8)	1 (0.6)	1 (0.7)	–	5 (2.5)
Eczema asteatotic	–	3 (1.8)	–	2 (1.5)	–	5 (2.5)
Dental caries	2 (1.0)	–	1 (0.6)	1 (0.7)	–	4 (2.0)
Sinusitis	–	2 (1.2)	2 (1.3)	–	–	4 (2.0)
Ligament sprain	1 (0.5)	1 (0.6)	1 (0.6)	1 (0.7)	–	4 (2.0)
Excoriation	1 (0.5)	2 (1.2)	1 (0.6)	–	–	4 (2.0)
Thermal burns	2 (1.0)	2 (1.2)	–	–	–	4 (2.0)
Skin papilloma	2 (1.0)	1 (0.6)	1 (0.6)	–	–	4 (2.0)
Hand dermatitis	–	1 (0.6)	1 (0.6)	2 (1.5)	–	4 (2.0)
Any bilastine-related adverse events						
Aspartate aminotransferase increased	–	–	–	–	1 (0.8)	1 (0.5)
γ-Glutamyltransferase increased	1 (0.5)	–	–	–	–	1 (0.5)
Somnolence	2 (1.0)	–	–	–	–	2 (1.0)
Nocturia	1 (0.5)	–	–	–	–	1 (0.5)

Analysis set was safety analysis set. AE occurring in 2% or more of patients and all adverse drug reactions are shown. Data included the treatment period and the continued treatment period. AE, adverse events.

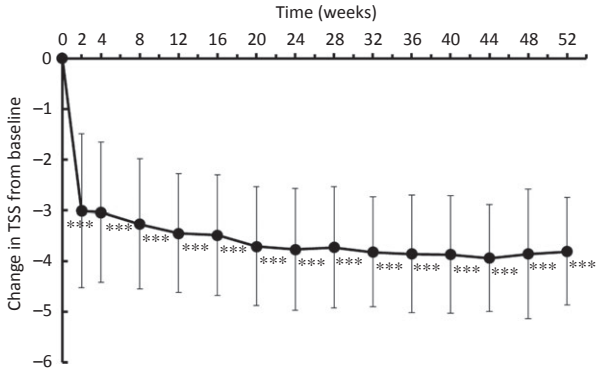

Figure 2. Change in total symptom score from baseline through the 52-week treatment period for chronic spontaneous urticaria. Each datum represents the mean and standard deviation. ***$P < 0.001$ versus baseline (paired *t*-test). TSS, total symptom score.

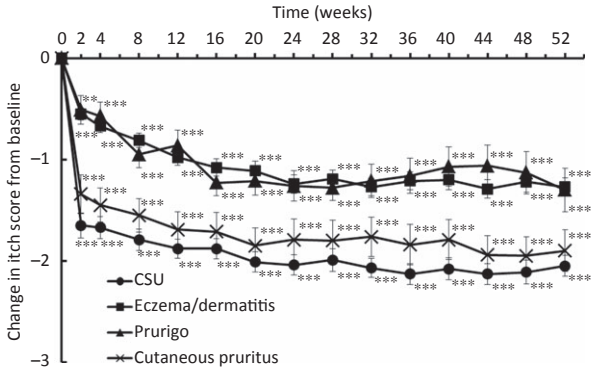

Figure 3. Change in itch score (average of daytime and nighttime) from baseline through the 52-week treatment period for chronic spontaneous urticaria and pruritus associated with skin diseases (eczema/dermatitis, prurigo and cutaneous pruritus). Each datum represents the mean and standard deviation. **$P < 0.01$, ***$P < 0.001$ versus baseline (paired *t*-test). CSU, chronic spontaneous urticaria.

DISCUSSION

We conducted this open-label, multicenter study to evaluate the safety and efficacy of once-daily administration of bilastine 20 mg for up to 52 weeks in patients with CSU or pruritus associated with skin diseases. To the best of our knowledge, this is the first study to evaluate the long-term safety and efficacy of 1-year H_1-antihistamine treatment in Japanese patients with CSU or pruritus associated with skin diseases.

The overall treatment compliance rate in the safety analysis set was 98.05%, and there were no differences among the disease types (97–99%). These results indicate that the compliance to long-term treatment with bilastine is very good.

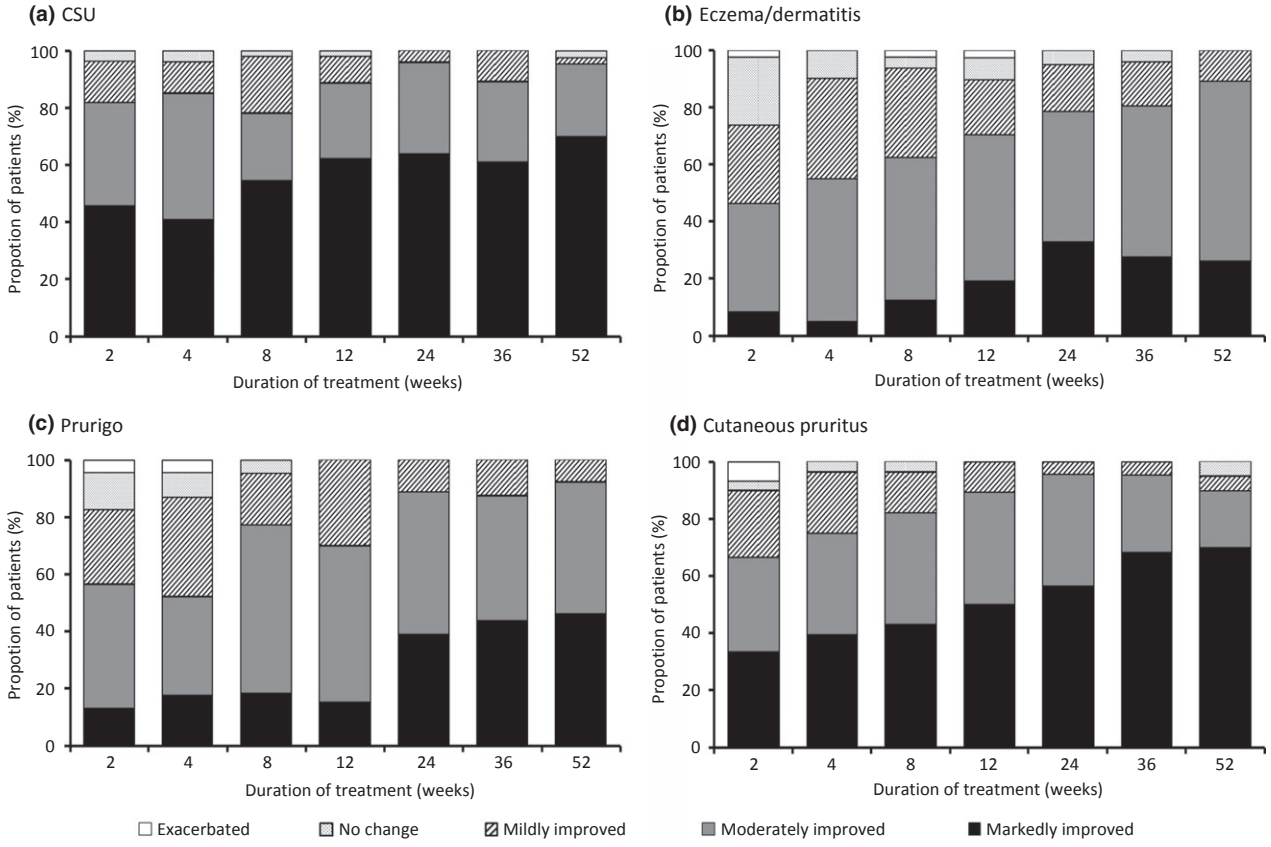

Figure 4. Overall improvement during treatment (investigator assessment). The intensity of itch and/or rash was classified as markedly improved, moderately improved, mildly improved, no change or exacerbated, absent for patients present (patient diary and clinical observations) at the visit for (a) CSU, and pruritus associated with skin diseases ([b] eczema/dermatitis, [c] prurigo and [d] cutaneous pruritus). CSU, chronic spontaneous urticaria.

None of the patients died during the study. Three patients experienced serious AE (retinal detachment, lumber fracture and cervical epithelial dysplasia); however, these were judged by the investigators not to be related to bilastine. Three patients discontinued the treatment owing to AE (oropharyngeal pain, eczema and asthma), which were also not related to bilastine, according to the investigator's assessment. The overall incidence of bilastine-related AE was only 2.5% (5/197 patients) over the 52-week treatment: somnolence in 1.0% (2/197), and increased aminotransferase aspartate, increased γ-glutamyltransferase and nocturia in 0.5% (1/197) of patients each. No increase in the incidence of AE/bilastine-related AE and no suspected late-onset AE were noted in association with the extended treatment duration. No clinically significant change or abnormality was noted in laboratory tests or vital signs. An overseas clinical study of long-term treatment with bilastine 20 mg once daily for 1 year was conducted in patients with perennial AR.[20] Although the diseases targeted in the present study were different from those in the overseas study, this study showed no AE or bilastine-related AE specific to Japanese patients when compared with the overseas study. These results suggest that long-term treatment with bilastine 20 mg once daily for 1 year is safe and is well tolerated in Japanese patients with CSU or pruritus associated with skin disease.

We conducted a randomized, placebo-controlled phase II/III study in Japanese patients with CSU, which clearly demonstrated that bilastine 20 mg once daily for 2 weeks was superior to placebo in efficacy based on the TSS.[14] The overseas phase III study in patients with CSU corroborated that the efficacy of bilastine 20 mg was superior to that of placebo and comparable to that of levocetirizine 5 mg.[21] Accordingly, this study clearly demonstrated that bilastine 20 mg once daily is effective in patients with CSU. Assessment results for efficacy variables in CSU in this study were completely in line with those of the phase II/III study in Japanese patients with CSU. When we compared the efficacy variables of bilastine 20 mg in CSU among the studies, change in TSS from baseline at week 2 was -3.01 ± 1.52 versus -3.02 ± 1.63 (present vs phase II/III study), and the change in itch score (average of daytime and nighttime) was -1.65 ± 0.91 versus -1.64 ± 0.99. Although the study design was completely different between both trials (open vs double-blind, placebo-controlled), the efficacy of 2-week treatment was the same in the present and the phase II/

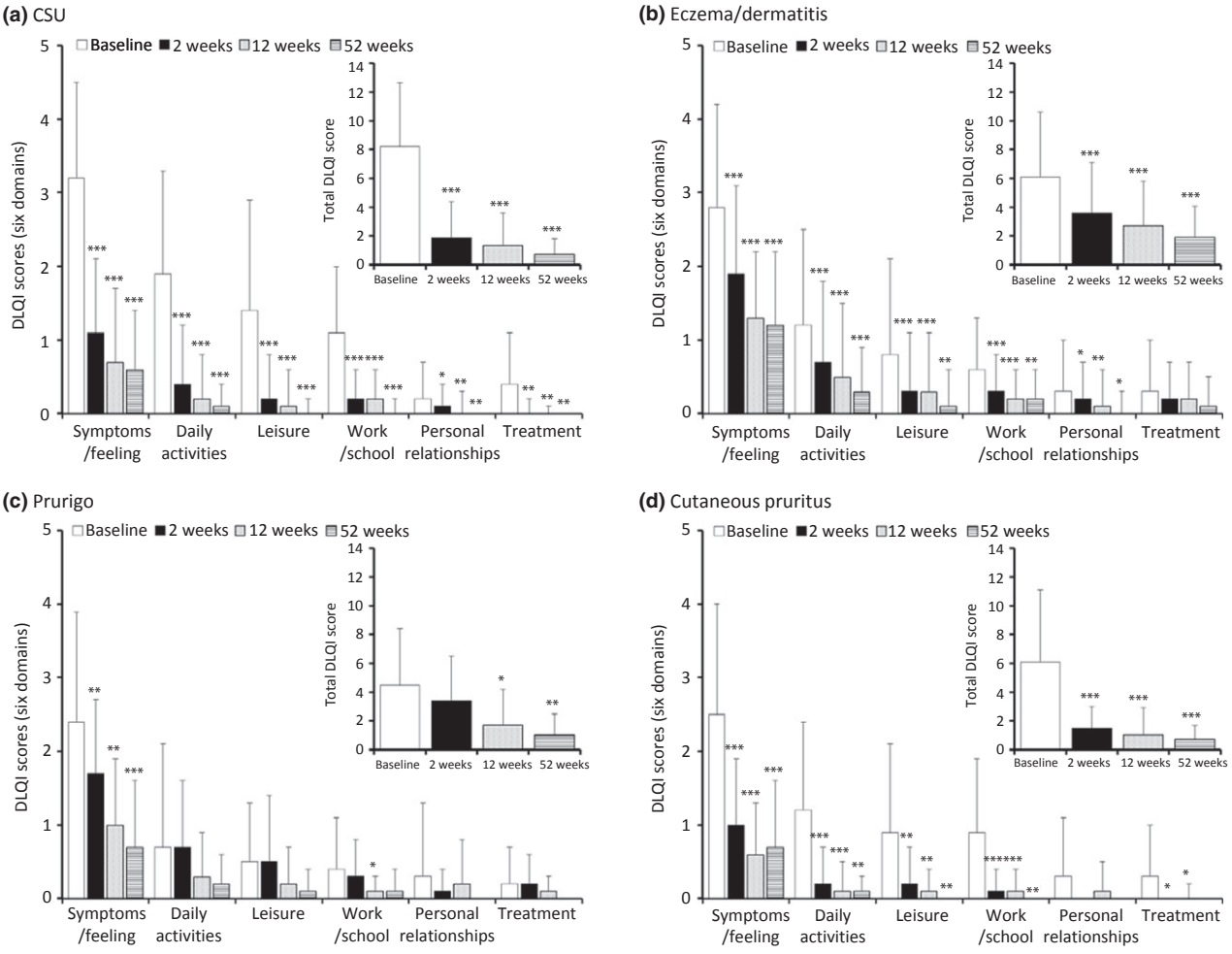

Figure 5. Total quality of life score and individual domain (symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment) scores at baseline, 2 weeks, 12 weeks and 52 weeks for (a) CSU, and pruritus associated with skin diseases ([b] eczema/dermatitis, [c] prurigo and [d] cutaneous pruritus). Error bars represent the standard deviation. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus baseline (paired *t*-test). CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index.

III study. Although various bias effects might have affected the efficacy evaluation in patients and investigators owing to the fact that this was an open study, we conclude that the long-term efficacy of bilastine could be evaluated in the present study.

With respect to long-term efficacy in patients with CSU, bilastine 20 mg once daily significantly improved TSS, itch, rash and QOL scores during the 52-week treatment as compared with the baseline scores. Improvement in TSS, itch and rash scores was observed early in the treatment (days 1–3). In addition, markedly improved or moderately improved ratings were noted for over 80% of patients at every assessment by the investigators.

Similar results were obtained in patients with pruritus associated with skin diseases. Briefly, bilastine 20 mg once daily significantly improved itch and QOL score during the 52-week treatment. Improvement in itch score was also observed early in the treatment (days 1–3). In addition, investigator's rash score for eczema/dermatitis or prurigo improved during the 52-week treatment. Concomitant use of topical corticosteroids (weak, medium or strong rank) was permitted in these groups; more than 90% of patients actually used topical corticosteroids. Therefore, in addition to the effect of bilastine on the scratching behavior at skin lesions, an effect of the use of topical corticosteroids should be also taken into account when considering the improvement in itch scores. On the other hand, there were some differences in efficacy for itch among the diseases. Although significant improvement in the itch score was observed for all diseases at each assessment point, the change from baseline was larger in patients with CSU or in the cutaneous pruritus group than in those with eczema/dermatitis or prurigo (Fig. 3). It is generally known that histamine has different effects on itch in different CP disease types; moreover, histamine H_1-receptor-induced itch in patients with conditions

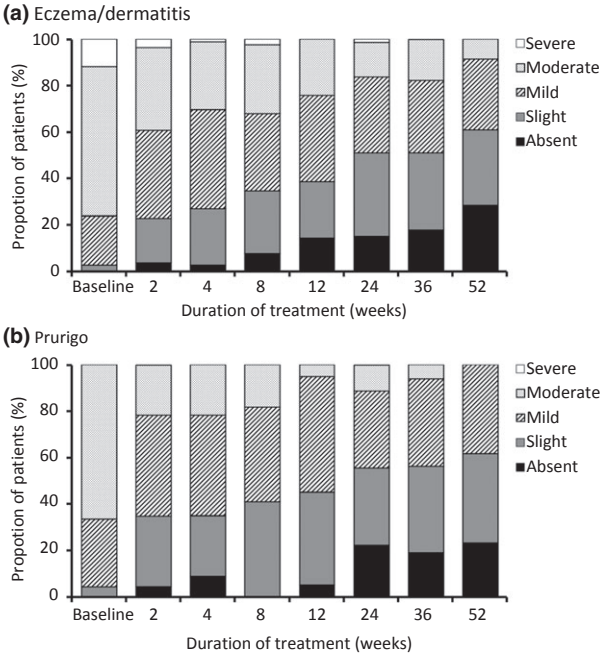

Figure 6. Rash scale for investigator assessment. The intensity of rash was classified as absent, slight, mild, moderate or severe for patients present at the visit for pruritus associated with (a) eczema/dermatitis or (b) prurigo.

including atopic dermatitis, prurigo or cutaneous pruritus is lower than that in patients with CSU.[6,22] Because there were no significant differences in the baseline scores between groups, we reason that the decrease in itch scores can be ascribed to the degree of involvement of histamine in diseases. In consistence herewith, it was previously reported that second-generation H_1-antihistamine is effective for itch in patients with CP.[3,23,24] In addition, markedly improved or moderately improved ratings showed higher tendency to depend on the treatment duration. Therefore, we can conclude that bilastine is effective in patients with CSU or pruritus associated with skin diseases, and efficacy is maintained for 52 weeks with no loss of drug sensitivity at a regime of 20 mg once daily.

This study was designed as an open-label trial. Based on a systematic published work review, Zuuren *et al.*[25] reported that there currently is a lack of evidence to support or refute the use of H_1-antihistamines alone in the management of eczema. A placebo-controlled study would be necessary to evaluate the long-term safety and efficacy of bilastine in Japanese patients more accurately. However, no apparent changes or abnormalities in laboratory tests and vital signs, which are objective indicators, were noted, providing a rationale for long-term safety of bilastine. This study included only 16 patients aged 65 years or older. Because the elderly are affected with a variety of skin diseases due to aging-related decrease of skin barrier and change of treatment response, the safety and efficacy of bilastine needs to be evaluated in elderly patients.

In summary, no safety concern was identified during the 52-week treatment with bilastine 20 mg administrated once daily in patients with CSU or pruritus associated with skin diseases, suggesting that long-term treatment with bilastine is safe and well tolerated in Japanese patients. Bilastine improved CSU or pruritus associated with skin diseases early in the treatment, and the efficacy was maintained throughout the treatment duration.

ACKNOWLEDGMENTS: We thank the study investigators and assistants at the investigative clinics: Ryuta Ono (Kanagawa Himawari Clinic), Hideki Ito (Tachikawa Dermatology Clinic), Tatsuya Izumi (Hiroo Dermatology Clinic), Yoshihiko Furui (Kawaguchi Dermatology Clinic), Kazutomo Toyofuku (Yamate Dermatological Clinic), Toshiya Asai (Asai Dermatology Clinic), Meiko Tsunoda (Tsunoda Clinic), Naoko Motohashi (Akemi Dermatology Clinic), Shigeru Hanawa (Oizumi Hanawa Clinic), Kanbe Yuki (Shakaiiryohouzinzaidansekishinkai Sayama General Clinic), Keizo Matsuo (Matsuo Clinic), Tetsuo Matsuda (Matsuda Dermatology Clinic), Akito Toshitani (Toshitani Dermatology Clinic), Masahiro Kusuhara (Kusuhara Dermatology Clinic) and Aisaku Yamamoto (Kosugi Dermatology Clinic). We also thank the Quintiles Transnational Japan, Tokyo and Osaka, for the management, monitoring and statistical analysis of the data, and Shigeyuki Koizumi (TAIHO Pharmaceutical, Tokyo, Japan) who played an overall management role in the study. The authors acknowledge Drs Lourdes Azcárate, Román Valiente, and Luis Labeaga (FAES FARMA, Spain) for the scientific review of the manuscript. This study was funded by TAIHO Pharmaceutical, Tokyo, Japan.

CONFLICT OF INTEREST: A. Y. and M. F. have no conflict of interest with respect to the content of this article. M. T. and A. S. are employees of TAIHO Pharmaceutical. M. H. received lecture and/or consultation fees from TAIHO Pharmaceutical, Novartis, MSD, Teikoku Seiyaku and Mitsubishi Tanabe Pharma Co.

REFERENCES

1 Erturk IE, Arican O, Omurlu IK, Sut N. Effect of the pruritus on the quality of life: a preliminary study. *Ann Dermatol* 2012; **24**: 406–412.
2 Carr CW, Veledar E, Chen SC. Factors mediating the impact of chronic pruritus on quality of life. *JAMA Dermatol* 2014; **150**: 613–620.
3 Murota H, Kitaba S, Tani M *et al.* Impact of sedative and non-sedative antihistamines on the impaired productivity and quality of life in patients with pruritic skin diseases. *Allergol Int* 2010; **59**: 345–354.
4 Ständer S, Weisshaar E, Mettang T *et al.* Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007; **87**: 291–294.
5 Metz M, Ständer S. Chronic pruritus-pathogenesis, clinical aspects and treatment. *J Eur Acad Dermatol Venereol* 2010; **24**: 1249–1260.
6 Hide M, Hiragun T. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. *Allergol Int* 2012; **61**: 517–527.
7 Zuberbier T, Aberer W, Asero R *et al.* The EAACI/GA^2 LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**: 868–887.
8 Bernstein JA, Lang DM, Khan DA *et al.* The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014; **133**: 1270–1277.
9 Weisshaar E, Szepietowski JC, Darsow U *et al.* European guideline on chronic pruritus. *Acta Derm Venereol* 2012; **92**: 563–581.

10 Saeki H, Nakahara T, Tanaka A *et al.* Clinical practice guidelines for the management of atopic dermatitis 2016. *J Dermatol* 2016; **43**: 1117–1145.
11 Farré M, Pérez-Mañá C, Papaseit E *et al.* Bilastine vs. hydroxyzine: occupation of brain histamine H1 receptors evaluated by positron emission tomography in healthy volunteers. *Br J Clin Pharmacol* 2014; **78**: 970–980.
12 Tyl B, Kabbaj M, Azzam S *et al.* Lack of significant effect of bilastine administered at therapeutic and supratherapeutic doses and concomitantly with ketoconazole on ventricular repolarization: results of a thorough QT study (TQTS) with QT-concentration analysis. *J Clin Pharmacol* 2012; **52**: 893–903.
13 Lasseter KC, Sologuren A, La Noce A, Dilzer SC. Evaluation of the single-dose pharmacokinetics of bilastine in subjects with various degrees of renal insufficiency. *Clin Drug Investig* 2013; **33**: 665–673.
14 Hide M, Yagami A, Togawa M, Saito A, Furue M. Efficacy and safety of bilastine in Japanese patients with chronic spontaneous urticarial: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II/III study. *Allegol Int* 2016. doi: 10.1016/j.alit.2016.08.004.
15 Okubo K, Gotoh M, Asako M *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. *Allegol Int* 2017; **66**: 97–105.
16 International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, 1995.
17 Kawashima M, Kukita A, Harada S *et al.* [The efficacy and safety of SCH 29851 (loratadine), a long acting and selective histamine H1 receptor antagonist, for chronic urticaria in a phase III, randomized, double-blind, multi-center comparative study: investigation of superiority of SCH 29851 10 mg once daily to SCH 29851 1 mg once daily and of non-inferiority of SCH 29851 10 mg once daily to ketotifen fumarate 1 mg twice daily]. [*J Clin Therap Med*] 2002; **18**: 881–905 (in Japanese).
18 DLQI Instructions for use and scoring. [Cited 8 May 2014] Available from URL: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/.
19 Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.
20 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**: 121–130.
21 Zuberbier T, Oanta A, Bogacka E *et al.* Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. *Allergy* 2010; **65**: 516–528.
22 Weisshaar E, Kucenic MJ, Fleischer AB Jr. Pruritus: a review. *Acta Derm Venereol Suppl (Stockh)* 2003; **213**: 5–32.
23 Kawashima M, Tango T, Noguchi T *et al.* Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. *Br J Dermatol* 2003; **148**: 1212–1221.
24 Wang T, Liu Y, Yin J *et al.* A multicenter, double-blind, randomized, noninferiority comparison of 14 days' treatment with oral olopatadine 10 mg or cetirizine 10 mg in Chinese adults with cutaneous pruritus. *Pharmacology* 2013; **91**: 117–122.
25 van Zuuren EJ, Apfelbacher CJ, Fedorowicz Z, Jupiter A, Matterne U, Weisshaar E. No high level evidence to support the use of oral H1 antihistamines as monotherapy for eczema: a summary of a Cochrane systematic review. *Syst Rev* 2014; **3**: 25.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Rank of topical corticosteroids

Table S2. Itch scale

Table S3. Rash scale

Table S4. Scale used by the investigators for assessment of overall improvement.

Table S5. Rash scale used by the investigators.