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 chronic spontaneous urticaria: A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II/III study

Michihiro Hide [a, *], Akiko Yagami [b], Michinori Togawa [c], Akihiro Saito [c], Masutaka Furue [d]

[a] Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[b] Department of Dermatology, School of Medicine, Fujita Health University, Aichi, Japan
[c] Clinical Development Division, Taiho Pharmaceutical Co., Ltd., Tokyo, Japan
[d] Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form
24 July 2016
Accepted 1 August 2016
Available online xxx

Keywords:
Bilastine
Chronic spontaneous urticaria
DLQI
H_1-antihistamine
Total symptom score

Abbreviations:
ANCOVA, analysis of covariance; CI, confidence interval; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; FAS, full analysis set; QOL, quality of life; SP, safety population; TSS, total symptom score

ABSTRACT

Background: Bilastine, a novel non-sedating second-generation H_1-antihistamine, has been widely used in the treatment of allergic rhinoconjunctivitis and urticaria with a recommended dose of 20 mg once daily in most European countries since 2010. We evaluated its efficacy and safety in Japanese patients with chronic spontaneous urticaria (CSU).

Methods: We conducted a multicenter, randomized, double-blind, placebo-controlled phase II/III study (trial registration No. JapicCTI-142574). Patients (age, 18–74 years) were randomly assigned to receive bilastine 20 mg, 10 mg or placebo once daily for 2 weeks. The primary efficacy endpoint was the change from baseline (Day −3 to 0) in total symptom score (TSS) at 2 weeks (Day 8–14), consisting of the itch and rash scores.

Results: A total of 304 patients were randomly allocated to bilastine 20 mg (101 patients), bilastine 10 mg (100 patients), and placebo (103 patients). The changes in TSS at 2 weeks were significantly decreased by bilastine 20 mg than did placebo ($p < 0.001$), demonstrating the superiority of bilastine 20 mg. Bilastine 10 mg also showed a significant difference from placebo ($p < 0.001$). The TSS changes for the bilastine showed significant improvement from Day 1, and were maintained during the treatment period. The Dermatology Life Quality Index scores were also improved in bilastine than in placebo. The bilastine treatments were safe and well tolerated.

Conclusions: Two-week treatment with bilastine (20 or 10 mg) once daily was effective and tolerable in Japanese patients with CSU, demonstrating an early onset of action.

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Introduction

Urticaria is one of the most common skin diseases, and the management of this disease is important because it often causes a high impairment in the quality of life (QOL).[1] Urticaria is characterized by the appearance of itchy wheals and flare that usually disappear in hours. The lifetime prevalence of chronic spontaneous urticaria (CSU), defined as episodic or daily hives lasting for 6 weeks, occurs in approximately 1.8% of the adult population with a period prevalence (past 12 months) of 0.6%–0.8%.[2,3]

In the Japanese guideline for the diagnosis and treatment of urticaria[4] published by the Japanese Dermatological Association in 2011, CSU is defined as the persistence of urticaria for >1 month without apparent involvement of triggers. This guideline also described two principles for treating urticaria: (i) removing or avoiding causative and/or aggravating factors, and (ii) using medications including H_1-antihistamines. Concerning medications for the treatment of urticaria, the guideline states that oral H_1-antihistamines may be used as a mainstay treatment for virtually all subtypes of urticaria. However, the efficacy of H_1-antihistamines in treating urticaria is largely variable among subtypes, or individual patients. Therefore, the aims and nature of the treatment for urticaria should be planned, taking into consideration the subtype and severity of urticaria as well as the specific conditions of individual patients. The guideline also recommends second-generation H_1-antihistamines, which have little penetration into the central

* Corresponding author. Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail address: ed1h-w1de-road@hiroshima-u.ac.jp (M. Hide).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.08.004
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nervous system and low sedative properties, as the first-line in drug therapy. For symptomatic relief, non-sedating H_1-antihistamines are also the first choice for most subtypes of urticaria in a recent worldwide guidance/guideline for the management of CSU.[5,6]

Bilastine has shown high affinity and selectivity for histamine H_1 receptors, and a potent anti-allergic activity in preclinical studies.[7,8] An overseas clinical study in patients with seasonal allergic rhinitis demonstrated that a single administration of bilastine 20 mg showed a rapid onset of action (60 min), and maintained its efficacy for >24 h.[9] Moreover, bilastine requires no dose adjustment for patients with renal impairment.[10] It has been also reported that a single oral dose of bilastine 20 mg had minimal H_1 histamine receptor occupancy in the brain (mean value, −3.92%), and was categorized as a non-sedating antihistamine according to the positron emission tomography criteria.[11] In addition, bilastine has been confirmed not to affect driving activity at a dose of 20 mg, or even 40 mg, in a driving test.[12] Although bilastine at therapeutic and supratherapeutic doses (20 mg and 100 mg once daily, respectively) had no clinically significant impact on QTc prolongation in electrocardiogram.[13] Although bilastine has been authorized and used to treat allergic rhinitis and urticaria with a recommended dose of 20 mg once daily in patients aged 12 years or older, in most countries in Europe since 2010, it has not been approved in Japan.

We conducted a multicenter, randomized, double-blind, placebo-controlled phase II/III study to evaluate the efficacy, safety, and dose-response of bilastine at doses of 10 and 20 mg, administered once a day for 14 days, in Japanese patients with CSU.

Methods

Study design

This study, conducted at 44 centers in Japan, was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase II/III study in patients with CSU. The primary objectives of this study were to verify the superiority of bilastine 20 mg over placebo by using the total symptom score (TSS), and also to investigate the dose-response of bilastine at doses of 10 and 20 mg.

Eligible patients entered a 4- to 14-day run-in period. A total of 300 patients were planned to be randomized (1:1:1) into one of the three treatment arms: bilastine 10 mg, bilastine 20 mg, or placebo. For all active treatments and placebo, the tablets (supplied by Taiho Pharmaceutical, Tokyo, Japan) had identical appearances to maintain the double-blind status. A nondeterministic minimization method was applied to the randomization of patients. The factors in the dynamic allocation were severity (<25 and ≥25 points as the sum of the itch [the sum of daytime and nighttime scores] and the rash [synthetic] scores for 3 days before randomization), and age (≥65 and <65 years). Randomization was done centrally through a computer (ADJUST, Sapporo, Japan). The day after randomization was set as the first day of drug administration (Day 1). The study drug was administered once daily in the morning, within 1 h before or 2 h after breakfast, for 2 weeks. A follow-up visit was scheduled 4–7 days after the end of the treatment. Patients who completed all of their visits including the follow-up were considered to have completed the study.

Patients

Male and female patients, 18–74 years old, with a documented history of CSU, characterized by erythematous skin wheals of unknown etiology, occurring regularly from 4 weeks or more before consent acquisition, were recruited. Eligible patients for registration were required to demonstrate a symptom score of at least 8 (maximum score: 24) as the sum of the itch score (sum of daytime and nighttime), and at least 5 (maximum score: 9) as the sum of the rash (synthetic) score during the last 3 days before registration in the run-in period. Patients were required to record every symptom scores on the patient diary for the last 3 days before registration and to record the symptom scores more than 80% in whole the ruin-in period.

Patients were excluded from the study if they had any dermatological condition that could interfere with the efficacy evaluation (including eczema, contact dermatitis, atopic dermatitis, nummular eczema, autosensitization dermatitis, pompholyx, asteatotic eczema, lichen simplex chronicus, 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 known hypersensitivity to antihistamine, any clinically significant condition (cardiovascular, neurological, hepatic, renal, or malignant diseases), or received ultraviolet light therapy before entry. Similarly, patients who had received antihistamines (including H_2 receptor antagonists, excluding ebastine), anti-allergy drugs, nonsteroidal anti-inflammatory drugs, neurotropin, antiplasmin drugs (tranexamic acid), glycyrrhizinate, diaminodiphenyl sulfone, psychotropic drugs (antipsychotic drugs, antidepressants, sleeping pills, or antianxiety drugs), antipruritic drugs (pregabalin or crotamiton), or drugs for the target diseases (including Kampo medicines) in the previous 6 days; ebastine in the previous 7 days; corticosteroids (excluding depot formulations), tacrolimus hydrate, immunological drugs (methotrexate, cyclophosphamide, mycophenolate mofetil, or omalizumab), or estrogen in the previous 21 days; corticosteroids (depot formulations), P-glycoprotein inhibitors (ketoconazole, erythromycin, cyclosporine, or diltiazem), specific immunotherapy, or nonspecific modulation therapy in the previous 30 days; or investigational drugs in the previous 90 days before randomization were excluded.

Efficacy assessments

The primary endpoint was the change from baseline in TSS, defined as the sum of the rash (synthetic) and itch (mean of daytime and nighttime) scores, at Week 2 (mean score for Day 8–14 after the first drug administration). The baseline values were the average score during the four consecutive days before the first drug administration (Day -3–0).

We also evaluated the change from baseline in TSS at Day 1–3 (mean score for 3 days) and Week 1 (mean score for Day 1–7 after the drug administration) as a secondary endpoint. Similar to TSS, the rash (synthetic, flare, and wheal) score and the itch (daytime and nighttime) score were evaluated.

The patients assessed their rash score every day by using a four-point scale (0–3) for the synthetic score, and wheal score (Supplementary Table 1). The patients assessed their itch score (daytime and nighttime) every day by using a five-point scale (0–4) (Supplementary Table 2). In addition, the patients assessed their QOL by using the Japanese version of the Dermatology Life Quality Index (DLQI; ©Dermatology Life Quality Index. A.Y. Finlay, G.K. Khan, April 1992)[14] at the randomization visit (Day 0), at Day 7, and at the end of treatment (Day 14), or at the early discontinuation visit in case of withdrawal from the study. The DLQI questionnaire was a self-administered QOL instrument comprising 10 questions (each of which is rated on a four-point scale: 0, not at all; 1, a little; 2, a lot; and 3, very much; a not relevant response was also scored as 0). The DLQI measures the effect of CSU on six domains:

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symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment inconveniences. The DLQI was summarized by using the overall or individual domains, with summing of the scores for each question; a higher score indicated greater impairment in the QOL of the patient. The DLQI has been shown to be reproducible, valid, and responsive for measuring disease-related QOL.[15] We obtained permission to use DLQI assessment from Drs. A.Y. Finlay and G.K. Khan (Department of Dermatology, Cardiff University School of Medicine) before conducting this study.

At each patient visit, the investigator evaluated the overall improvement according to patient diaries and physical examination by using a five-point scale (1, markedly improved; 2, moderately improved; 3, mildly improved; 4, no change; 5, exacerbated; Supplementary Table 3).[16]

Safety assessments

Safety was assessed on the basis of the incidence and severity of adverse events (AEs), laboratory tests (clinical chemistry and hematology), and vital signs (blood pressure, body temperature, and heart rate). AEs were monitored during the treatment and follow-up periods. The causal relationships for all AEs were categorized by the investigator as probable, possible, unlikely, or unrelated. Treatment compliance was assessed through patient diary card recording.

Statistical analyses

The objective of this study was to verify the superiority of bilastine 20 mg over placebo as the primary efficacy endpoint for the full analysis set (FAS) population. A sample size of 270 patients (90 patients 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 0.83 points and a standard deviation of 1.7 points, based on a previous study.[17] Assuming that approximately 10% of the patients might withdraw from the study, the final sample size was calculated to be 300 patients (100 patients per arm).

Efficacy analyses were performed for the FAS of patients who were randomized to a treatment, received at least one dose of the study medication, and completed at least 4 days of diary assessments of TSS (Day 8−14) after receiving the study medication. For the primary efficacy endpoint, the superiority of bilastine 20 mg over placebo was analyzed by using an analysis of covariance (ANCOVA) model including treatment as a factor and baseline as a covariate. For the secondary analyses of the primary efficacy endpoint, dose-response was analyzed by using an ANCOVA model including treatment with contrast coefficients as a factor and baseline as a covariate. For the secondary efficacy endpoints of the overall evaluation of response to therapy and the change in DLQI score, summary statistics were calculated for each treatment group and compared between groups.

The changes from the baseline in TSS and each symptom score were analyzed by using an ANCOVA model. We analyzed TSS (the primary endpoint) by using age and severity (sum of the itch score during 3 days before registration [sum of daytime and nighttime scores as the daily score] and the rash [synthetic] score) as stratification factors.

Safety analyses were performed for the safety population (SP) of patients who received at least one dose of the study medication. The incidence of AEs and drug-related AEs was analyzed by using Fisher's exact tests.

All statistical analyses were performed with SAS software version 9.2 (SAS Institute, Cary, NC, USA). All reported p values were two-sided, and $p < 0.05$ was considered to be statistically significant.

Ethical approval and clinical trial registration

This trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by the Institutional Review Boards of all participating institutions. Informed consent was obtained from all participants included in the study. This study was registered with the Japan Pharmaceutical Information Center (no. JapicCTI-142574).

Results

Study population

Between July 2014 and November 2014, 339 patients were screened and 304 patients were randomized to one of the three treatment groups: 101 patients in the bilastine 20 mg, 100 patients in bilastine 10 mg and 103 patients in placebo (Fig. 1). Thirty-five patients were excluded from the study for not meeting the inclusion criteria (n = 21), according to the patient's decision (n = 8), and according to the investigator's judgment (n = 6). Of the randomized patients, 294 patients were included in the efficacy analysis (FAS) and 304 patients were included in the safety analysis (SP). Two hundred ninety-two patients (>96%) completed the study; 12 patients were withdrawn from the study (placebo: 9 patients, bilastine 20 mg: 2 patients, bilastine 10 mg: 1 patient). In detail, five patients withdrew their consent (placebo: 3 patients, bilastine 20 mg: 1 patient, bilastine 10 mg: 1 patient) and seven patients were withdrawn owing to a lack of efficacy as judged by the investigator (placebo: 6 patients, bilastine 20 mg: 1 patient).

The baseline demographic and clinical characteristics for the FAS population are summarized in Table 1. The number of female patients was significantly higher than that of males in all treatment groups. Statistically significant differences were found in patients' sex among the three groups ($p = 0.009$). The baseline demographic and clinical characteristics were otherwise similar among the treatment groups, with respect to age, body weight, and efficacy baseline value (TSS, rash [synthetic] score, itch [mean of daytime and nighttime] score, and DLQI score). The mean rate of treatment compliance was similar among the three treatment groups (99.33% in placebo, 98.97% in bilastine 10 mg, and 98.66% in bilastine 20 mg).

Efficacy

The results of primary efficacy endpoint are shown in Table 2. The estimated change from baseline in TSS at Week 2 was −3.01 (95% confidence interval [CI]: −3.27 to −2.75) in bilastine 20 mg and −1.49 (−1.75 to −1.22) in placebo. The estimated difference from placebo was −1.52 (−1.89 to −1.15), and there was a significant difference between bilastine 20 mg and placebo ($p < 0.001$), verifying the superiority of bilastine 20 mg over placebo in the primary efficacy endpoint. Analysis for the efficacy of bilastine 10 mg was performed according to a predefined statistical protocol. The estimated change from baseline in TSS at Week 2 was −3.23 (−3.48 to −2.98) in bilastine 10 mg, the estimated difference from placebo was −1.73 (−2.09 to −1.37); and the bilastine 10 mg showed significantly decreased TSS at Week 2 compared with placebo ($p < 0.001$). On the other hand, the estimated difference between bilastine 20 mg and 10 mg was 0.22 (−0.13 to 0.57); there was no significant difference between them ($p = 0.225$), taking into account that the efficacy of bilastine 10 mg was comparable to that of bilastine 20 mg in the primary endpoint (Table 2).

Next, the dose-response of bilastine in the primary efficacy endpoint was investigated by using the contrast test with contrast

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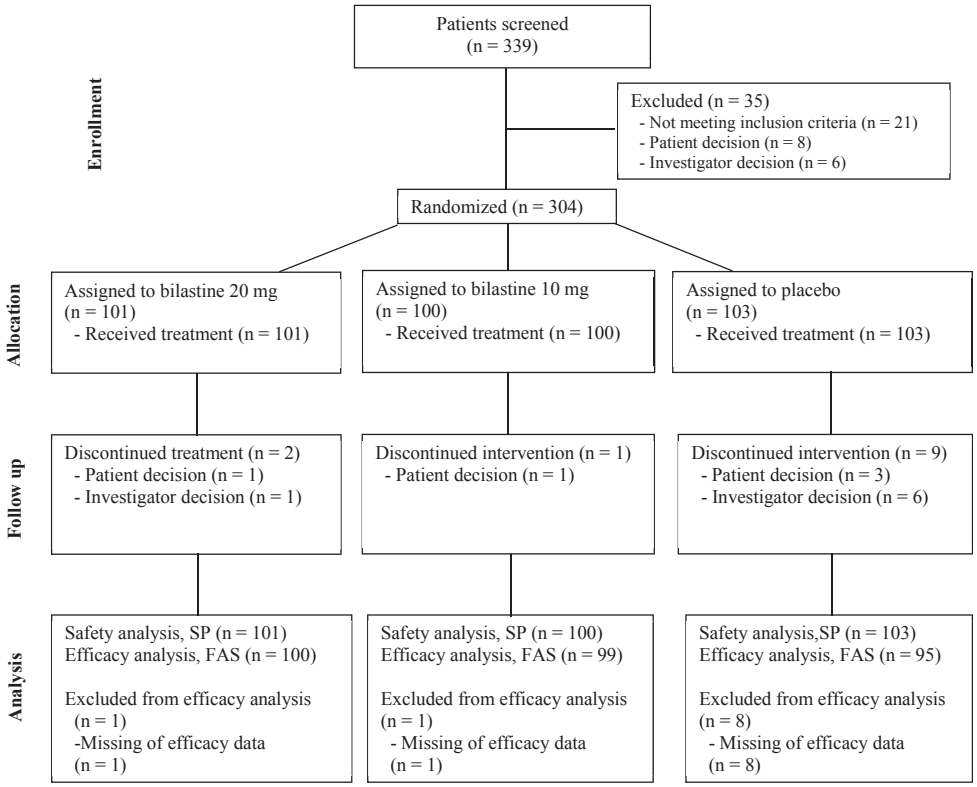


Fig. 1. Patient disposition. FAS, full analysis set; SP, Safety population.

Table 1
Patient demographics and characteristics at baseline (FAS).

Variable		Placebo (n = 95)	Bilastine 10 mg (n = 99)	Bilastine 20 mg (n = 100)	*p*-Value
Sex [n (%)]	Female	69 (72.6%)	83 (83.8%)	65 (65.0%)	0.009
	Male	26 (27.4%)	16 (16.2%)	35 (35.0%)	
Age (years) [mean ± SD]		39.7 ± 13.3	40.9 ± 12.9	42.0 ± 13.3	0.475
BW (kg/m^2) [mean ± SD]		58.0 ± 11.27	57.99 ± 11.69	60.55 ± 12.32	0.213
Baseline value [mean ± SD]					
TSS		4.49 ± 0.95	4.54 ± 0.91	4.54 ± 0.89	0.915
Itching (daytime and nighttime) score		2.44 ± 0.60	2.47 ± 0.62	2.47 ± 0.59	0.916
Rash (synthetic) score		2.05 ± 0.45	2.07 ± 0.42	2.07 ± 0.42	0.953
QOL score (total DLQI score)		7.5 ± 4.5	8.3 ± 5.0	8.0 ± 4.6	0.518

Analyzed with Fisher's exact test.
FAS, full analysis set; BW, body weight; DLQI, Dermatology Life Quality Index; QOL, quality of life; TSS, total symptom score.

coefficients of (1, 0, −1), (2, −1, −1), and (1, 1, −2) for the treatment groups (placebo, bilastine 10 mg, and bilastine 20 mg, respectively). No clear dose-relationship was observed by the contrast test ($p < 0.001$ in each contrast coefficients), however, each F-value in the contrast test was 69.884, 105.980, and 17.342 for the contrast coefficients (1, 0, −1), (2, −1, −1), and (1, 1, −2), respectively. The F-value by using (2, −1, −1) was greatest than with the others. The same results were obtained from the contrast test in the secondary endpoints (change in synthetic rash score and itch score at Week 2) (data not shown). These results suggested that the dose-response of bilastine might be close to the 10 mg dose saturation.

The results of the secondary efficacy endpoints are summarized in Table 3. The changes from baseline in TSS were greater in the bilastine groups than in the placebo across Day 1–3, Week 1, and Week 2 ($p < 0.001$ for bilastine 20 or 10 mg vs. placebo). The changes in rash (synthetic, flare, and wheal) scores and itch (daytime, nighttime, and mean of daytime and nighttime) scores were also greater in the bilastine groups than in the placebo from the early period of Day 1–3 through Week 2.

Figure 2 shows the changes from baseline in daily TSS (A), itch (B) and synthetic rash score (C). The daily TSS, itch, and rash score in placebo gradually decreased in a treatment day-dependent manner. The values for both bilastine 20 mg and 10 mg treatments dramatically decreased from Day 1 (first drug administration), and were maintained through Day 14. The changes from baseline in daily TSS, itch score, and rash score for the bilastine treatments showed significant differences during the treatment period in comparison with placebo (Student's t-test: $p < 0.001$, from Day 1–14).

It is well known that CSU has a significant impact on QOL. Therefore, we investigated the effect of bilastine on QOL in patients

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Table 2
Mean change from baseline in TSS at Week 2 (FAS).

(A) Primary analysis

		Bilastine 20 mg (n = 100)	Placebo (n = 95)
Baseline	Mean ± SD	4.54 ± 0.89	4.49 ± 0.95
Week 2	Mean ± SD	−3.02 ± 1.63	−1.47 ± 1.24
	Estimated change (95% CI)	−3.01 (−3.27 to −2.75)	−1.49 (−1.75 to −1.22)
	Estimated difference (95% CI)[†]	−1.52 (−1.89 to −1.15)	–
	p-Value vs. placebo	<0.001	–

(B) Secondary analysis

		Bilastine 20 mg (n = 100)	Bilastine 10 mg (n = 99)	Placebo (n = 95)
Baseline	Mean ± SD	4.54 ± 0.89	4.54 ± 0.91	4.49 ± 0.95
Week 2	Mean ± SD	−3.02 ± 1.63	−3.24 ± 1.45	−1.47 ± 1.24
	Estimated change (95% CI)	−3.01 (−3.26 to −2.76)	−3.23 (−3.48 to −2.98)	−1.50 (−1.75 to −1.24)
	Estimated difference (95% CI)[†]	−1.51 (−1.87 to −1.16)	−1.73 (−2.09 to −1.37)	–
	p-Value vs. placebo	<0.001	<0.001	–
	Estimated difference (95% CI)[‡]	0.22 (−0.13 to 0.57)	–	–
	p-Value vs. bilastine 10 mg	0.225	–	–

Analysis of covariance model including treatment as factor and baseline as a covariate.
Baseline: mean score of Day −3 to 0.
Week 2: mean score of Day 8–14.
TSS, total symptom score; FAS, full analysis set; CI, confidence interval.
[†] Estimated difference from placebo.
[‡] Estimated difference from bilastine 10 mg.

Table 3
Secondary efficacy endpoints: mean change from baseline in TSS, rash score, and itch score by treatment period (FAS).

			Placebo (n = 95)	Bilastine 10 mg (n = 99)	Bilastine 20 mg (n = 100)
TSS	Baseline	Mean ± SD	4.49 ± 0.95	4.54 ± 0.91	4.54 ± 0.89
	Day 1–3	Estimated change (95% CI)	−0.88 (−1.14 to −0.62)	−2.93 (−3.19 to −2.68)*	−2.62 (−2.87 to −2.37)*
	Week 1		−1.07 (−1.32 to −0.82)	−2.98 (−3.22 to −2.74)*	−2.74 (−2.98 to −2.50)*
	Week 2		−1.50 (−1.75 to −1.24)	−3.23 (−3.48 to −2.98)*	−3.01 (−3.26 to −2.76)*
Rash (synthetic) score	Baseline	Mean ± SD	2.05 ± 0.45	2.07 ± 0.42	2.07 ± 0.42
	Day 1–3	Estimated change (95% CI)	−0.44 (−0.57 to −0.31)	−1.31 (−1.44 to −1.18)*	−1.19 (−1.32 to −1.06)*
	Week 1		−0.54 (−0.67 to −0.42)	−1.33 (−1.45 to −1.20)*	−1.24 (−1.36 to −1.12)*
	Week 2		−0.72 (−0.85 to −0.60)	−1.44 (−1.57 to −1.32)*	−1.38 (−1.50 to −1.25)*
Rash (flare) score	Baseline	Mean ± SD	2.09 ± 0.50	2.08 ± 0.47	2.09 ± 0.50
	Day 1–3	Estimated change (95% CI)	−0.39 (−0.53 to −0.26)	−1.21 (−1.34 to −1.08)*	−1.12 (−1.26 to −0.99)*
	Week 1		−0.47 (−0.60 to −0.34)	−1.23 (−1.36 to −1.10)*	−1.17 (−1.30 to −1.04)*
	Week 2		−0.65 (−0.79 to −0.52)	−1.38 (−1.51 to −1.25)*	−1.32 (−1.45 to −1.19)*
Rash (wheal) score	Baseline	Mean ± SD	2.01 ± 0.62	1.92 ± 0.63	1.95 ± 0.66
	Day 1–3	Estimated change (95% CI)	−0.40 (−0.54 to −0.26)	−1.31 (−1.44 to −1.17)*	−1.22 (−1.36 to −1.09)*
	Week 1		−0.49 (−0.62 to −0.36)	−1.35 (−1.48 to −1.23)*	−1.29 (−1.42 to −1.17)*
	Week 2		−0.67 (−0.80 to −0.54)	−1.46 (−1.58 to −1.33)*	−1.41 (−1.54 to −1.28)*
Itch (mean of daytime and nighttime) score	Baseline	Mean ± SD	2.44 ± 0.60	2.47 ± 0.62	2.47 ± 0.59
	Day 1–3	Estimated change (95% CI)	−0.44 (−0.58 to −0.29)	−1.62 (−1.77 to −1.48)*	−1.43 (−1.57 to −1.29)*
	Week 1		−0.53 (−0.67 to −0.39)	−1.66 (−1.79 to −1.52)*	−1.50 (−1.63 to −1.36)*
	Week 2		−0.78 (−0.92 to −0.63)	−1.79 (−1.93 to −1.65)*	−1.63 (−1.77 to −1.50)*
Itch (daytime) score	Baseline	Mean ± SD	2.73 ± 0.66	2.78 ± 0.58	2.74 ± 0.64
	Day 1–3	Estimated change (95% CI)	−0.38 (−0.54 to −0.21)	−1.74 (−1.90 to −1.58)*	−1.53 (−1.69 to −1.37)*
	Week 1		−0.49 (−0.64 to −0.33)	−1.81 (−1.96 to −1.65)*	−1.62 (−1.77 to −1.47)*
	Week 2		−0.81 (−0.97 to −0.64)	−1.95 (−2.11 to −1.79)*	−1.81 (−1.97 to −1.65)*
Itch (nighttime) score	Baseline	Mean ± SD	2.15 ± 0.71	2.17 ± 0.83	2.21 ± 0.74
	Day 1–3	Estimated change (95% CI)	−0.50 (−0.65 to −0.35)	−1.51 (−1.66 to −1.36)*	−1.33 (−1.47 to −1.18)*
	Week 1		−0.57 (−0.71 to −0.42)	−1.51 (−1.65 to −1.37)*	−1.38 (−1.51 to −1.24)*
	Week 2		−0.74 (−0.88 to −0.60)	−1.63 (−1.77 to −1.49)*	−1.46 (−1.60 to −1.33)*

Analysis of covariance model including treatment as factor and baseline as a covariate.
*$p < 0.001$ for Bilastine 10 mg/20 mg vs. placebo.
Baseline: mean scores of Day −3 to 0.
Day 1–3: mean score for Day 1–3.
Week 1: mean score for Day 1–7.
Week 2: Mean score for Day 8–14.
FAS, full analysis set; CI, confidence interval.
Note: There was no significant difference between bilastine 10 mg and 20 mg.

with CSU by using DLQI. The results of DLQI (total DLQI score and individual domains score) are shown in Figure 3. The change from baseline in the total DLQI score at Day 14 was greater in the bilastine groups than in placebo (−6.4 ± 5.0, −7.2 ± 5.2, and −4.0 ± 3.9 in the bilastine 20 mg, 10 mg and placebo, respectively; $p < 0.001$ vs. placebo for both bilastine groups). Significant improvement of the total DLQI score by the bilastine treatments was also observed at Day 7 and the final assessment (data not

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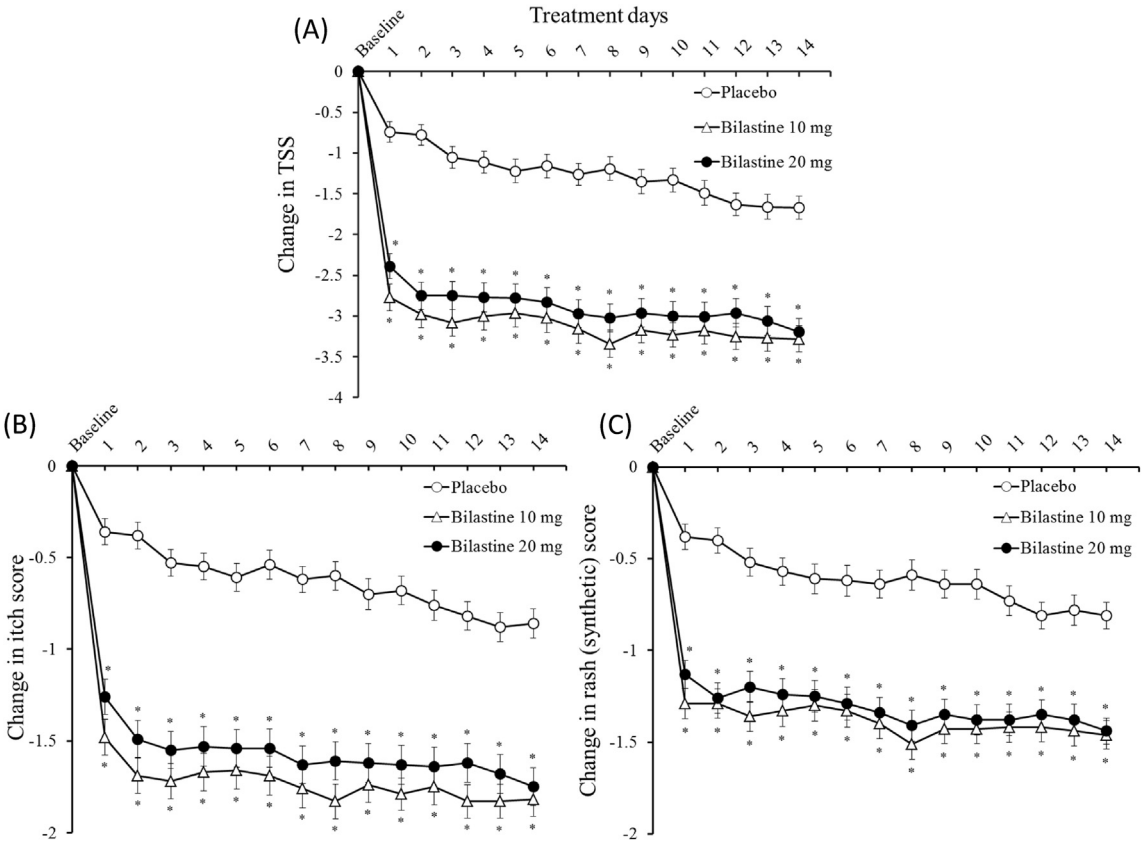


Fig. 2. Change from baseline in the daily total symptom score (**A**), daily itch score (**B**) or daily synthetic rash score (**C**) (FAS). Each datum represents the mean and SE. $^{*}p < 0.001$; vs. placebo in Student's *t*-test. FAS, full analysis set; TSS, total symptom score.

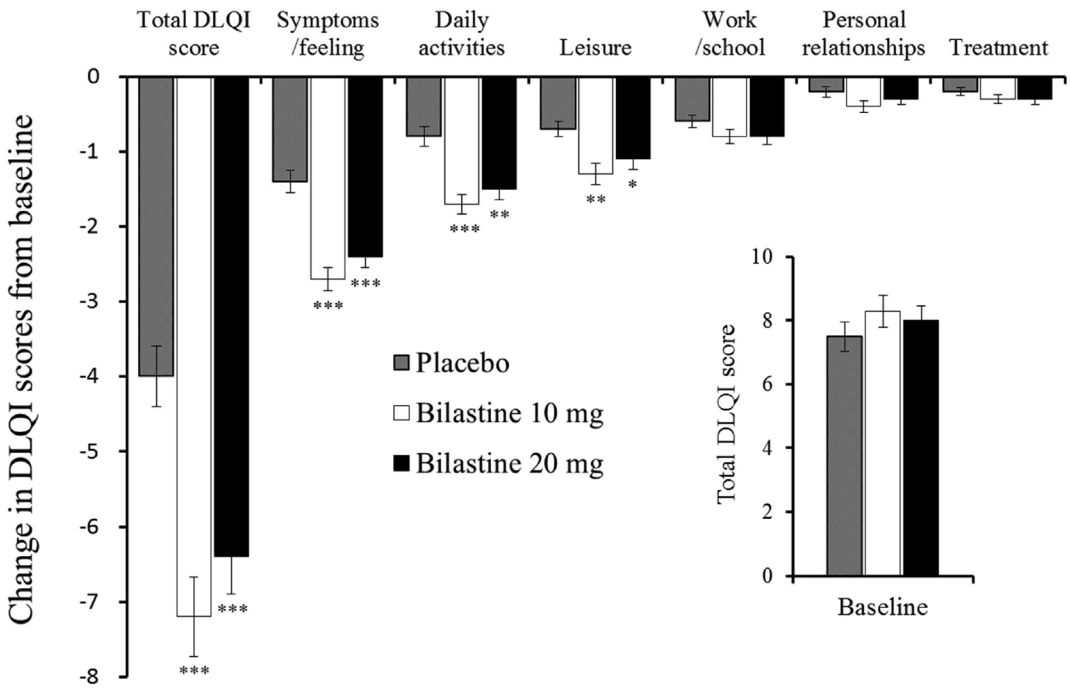


Fig. 3. Change from baseline in the DLQI score (FAS). DLQI scores indicate the sum of all scores (total DLQI) or categorization by the individual six domains including symptoms/feeling, daily activities, leisure, work/school, and personal relationship. Each datum represents the mean and SE. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, vs. placebo in Student's *t*-test. FAS, full analysis set; DLQI, Dermatology Life Quality Index.

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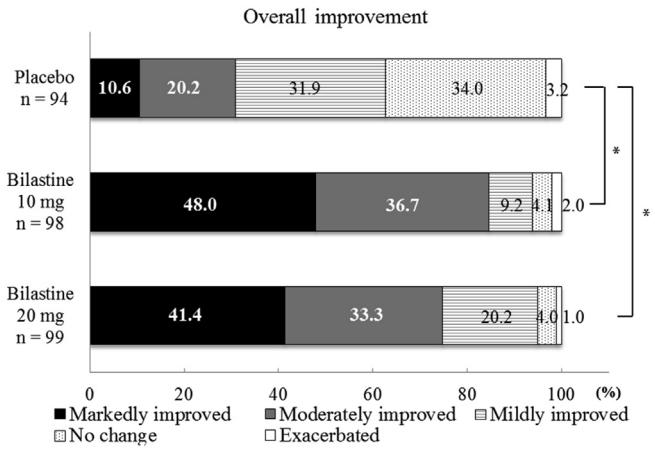


Fig. 4. Overall improvement as assessed by the investigators on Day 14 (FAS). *$p < 0.01$; vs. placebo in Fisher's exact test. FAS, full analysis set.

shown). When the individual six domains scores at Day 14 were investigated, the symptoms/feeling, daily activities, and leisure were significantly improved by bilastine 20 mg and 10 mg than by placebo.

Figure 4 shows the overall improvement on Day 14. The percentages of patients evaluated as improved (markedly improved plus moderately improved) by the investigator at Day 7, Day 14, and the final assessment were 71.0% (71/100), 74.7% (74/99), and 74.7% (74/99) in bilastine 20 mg; 78.8% (78/99), 84.7% (83/98), and 84.8% (84/99) in bilastine 10 mg; and 16.8% (16/95), 30.9% (29/94), and 31.6% (30/95) in placebo, respectively. There were significant differences between bilastine and placebo at all assessment time points (Fisher's exact test: $p < 0.001$).

Analysis of subgroups in the FAS

There were no significant differences in the change from baseline in TSS at Day 1–3, Week 1, and Week 2, or in the intergroup comparisons between the severity of CSU (<25 or ≥25 points as the sum of the itch [the sum of daytime and nighttime scores] and the rash [synthetic] score for 3 days before randomization), age (≥65 or <65 years), and sex (male or female) (data not shown).

Safety

Safety analyses were conducted in the SP, comprising 304 patients. The AEs reported during 2 weeks of treatment are summarized in Table 4. AEs reported during the study were of mild or moderate intensity, and of similar type and incidence across the three treatment groups. The proportions of patients with at least one AE and drug-related AE were similar across the groups (Fisher's exact test, AE; placebo vs. bilastine 20 mg: $p = 0.349$; placebo vs. bilastine 10 mg: $p = 0.497$; drug-related AE; placebo vs. bilastine 20 mg: $p = 1.000$; placebo vs. bilastine 10 mg: $p = 0.327$).

The most frequently reported AE in this study was nasopharyngitis. The incidence of AEs classified as nervous system disorders, which are class effects of H_1-antihistamines, was reported as follows: somnolence in 2.0% (2/100) in the bilastine 10 mg, and 2.9% (3/103) in placebo; headache in 2.0% (2/101) in bilastine 20 mg, 3.0% (3/100) in bilastine 10 mg, and 1.0% (1/103) in placebo; and dizziness and hypesthesia in 1.0% (1/100, each) in bilastine 10 mg. There were no serious AEs and no deaths. No patients withdrew as a result of AEs. Drug-related AEs were reported by two patients

Table 4
Adverse events reported during 2 weeks of treatment (SP).

	Placebo (n = 103) n (%)	Bilastine 10 mg (n = 100) n (%)	Bilastine 20 mg (n = 101) n (%)
Patients reporting ≥1 AE	20 (19.4%)	24 (24.0%)	14 (13.9%)
Incidence of AE† ≥2% in any treatment group	4 (3.9%)	5 (5.0%)	4 (4.0%)
Withdrawals due to AEs	0	0	0
Serious AEs	0	0	0
Nervous system disorders‡			
Dizziness†	0 (0.0%)	1 (1.0%)	0 (0.0%)
Headache†	1 (1.0%)	3 (3.0%)	2 (2.0%)
Hypesthesia†	0 (0.0%)	1 (1.0%)	0 (0.0%)
Somnolence†	3 (2.9%)	2 (2.0%)	0 (0.0%)
Drug-related AEs	3 (2.9%)	6 (6.0%)	2 (2.0%)
Gastrointestinal disorders‡	1 (1.0%)	3 (3.0%)	0 (0.0%)
General disorders and administration site conditions‡	2 (1.9%)	2 (2.0%)	0 (0.0%)
Investigations‡	0 (0.0%)	0 (0.0%)	1 (1.0%)
Nervous system disorders‡	1 (1.0%)	2 (2.0%)	1 (1.0%)
Headache†	0 (0.0%)	0 (0.0%)	1 (1.0%)
Somnolence†	1 (1.0%)	2 (2.0%)	0 (0.0%)

SP, safety population; AEs, adverse events.
† MedDRA (ver. 17.1) preferred term.
‡ MedDRA (ver. 17.1) system organ class.

(2.0%) in bilastine 20 mg, six patients (6.0%) in bilastine 10 mg, and three patients (2.9%) in placebo. The drug-related AEs reported were increased total bilirubin and headaches in bilastine 20 mg; somnolence, abdominal discomfort, constipation, nausea, fatigue, and dry mouth in bilastine 10 mg; and stomatitis, tooth pain, chest pain, dry mouth, and somnolence in placebo. There were no clinically significant changes from baseline values in any laboratory test, body temperature, heart rate, or systolic or diastolic blood pressure in any treatment group.

Discussion

This was the first randomized, double-blind, placebo-controlled, phase II/III study to evaluate the efficacy, safety, and dose-response of bilastine in Japanese patients with CSU. The patients took bilastine 20 mg, 10 mg, or matching placebo tablet once a day for 14 days.

Bilastine at a dose of 20 mg exhibited superiority over placebo with respect to the primary efficacy endpoint (the change from baseline in TSS at Week 2). Similar to bilastine 20 mg, bilastine 10 mg significantly decreased TSS than did placebo. There was no significant difference between the bilastine treatments. Similar results were obtained in the secondary efficacy endpoints. Accordingly, the dose-response of bilastine might be close to the 10 mg dose saturation in the present study. Our results on the dose-response of bilastine were similar to the previous results of the phase II study of bilastine in patients with CSU reported by Audicana *et al.*[18] These authors assessed the efficacy, safety, and dose-response of bilastine at doses of 10, 20, and 30 mg once daily for 4 weeks. As the result, all bilastine treatments showed a significant difference in the change from baseline in TSS (sum of pruritus severity, number of wheals, and maximum size of wheal scores) at 4 weeks in comparison with placebo, indicating that the dose-response of bilastine was not clear within the dose range of 10–30 mg. As it is well known that the efficacy of H_1-antihistamines on urticaria is largely variable among subtypes or individual patients,[4] further study may be necessary for patients with CSU refractory to recommended doses of antihistamines as done using

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other antihistamines, such as desloratadine and levocetirizine.[19] The results of the present study suggest that bilastine 10 mg is an effective dose for the treatment of general Japanese patients with CSU.

All symptom scores (TSS, rash [flare, wheal, and synthetic] scores, and itch [daytime, nighttime, and mean of daytime and nighttime] scores) were significantly improved from the early stage (Day 1–3) in the bilastine groups in comparison with placebo. In particular, the daily TSS, itch score, and synthetic rash score showed a significant decrease from Day 1 in the bilastine treatments (Fig. 2), indicating an early onset of action of bilastine for the treatment of CSU. The appropriateness of the dosage regimen of bilastine with a dosing of once a day could be confirmed with the comparison of daytime and nighttime itch scores in this study: (i) all patients took the study drug once a day in the morning; (ii) both bilastine 20 mg and 10 mg treatments significantly improved the daytime and nighttime itch scores at all assessment time points than did placebo; (iii) although the decreases in the estimated change in the daytime itch scores for the bilastine treatments were greater than those for the nighttime scores, the 95% CIs of the estimated difference from placebo in the bilastine treatments overlapped at all assessment time points (Table 3). Therefore, it could be concluded that the efficacy of once daily administration of bilastine continues throughout the day.

Additionally, we examined QOL by using the validated DLQI.[15] As a result, both bilastine treatments significantly improved the total DLQI score, as well as the individual domain scores, including symptoms/feeling, daily activities, and leisure (Fig. 3). To facilitate the clinical interpretation of the DLQI scores, a banding system has been suggested as follows: DLQI scores: 0–1 = no effect, 2–5 = small effect, 6–10 = moderate effect, 11–20 = very large, and 21–30 = extremely large effect.[20] The mean and SD of the total DLQI score at baseline was 8.0 ± 4.6 in bilastine 20 mg, 8.3 ± 5.0 in bilastine 10 mg, and 7.5 ± 4.5 in placebo. After 2 weeks of treatment, the total DLQI score was decreased to 1.6 ± 2.7 in bilastine 20 mg, 1.0 ± 1.7 in bilastine 10 mg, and 3.6 ± 2.9 in placebo. When the patients' QOL in treatments were classified by the mean of the total DLQI score according to this criteria, bilastine treatments changed to “no effect” on Day 14 from “moderate effect” at baseline (two-rank reduction). However, placebo treatment changed to “small effect” on Day 14 from “moderate effect” at baseline (one-rank reduction). In addition, Shikiar *et al.*[21] reported that the minimal important difference threshold for the DLQI in the range of 2.24–3.10 is recommended in interpreting the results for patients with CSU. The estimated difference from placebo in the total DLQI score was −2.5 (−3.7 to −1.2) in bilastine 20 mg and −3.2 (−4.5 to −1.9) in bilastine 10 mg; the differences in the bilastine treatments were fit in the beneficial threshold in the present Japanese study. These results suggested that bilastine at 20 or 10 mg was also effective in improving QOL in patients with CSU irrespectively of ethnicity.

The overall improvement has been used to investigate the efficacy of H_1-antihistamines in Japanese clinical studies for CSU. Accordingly, we used the overall improvement as judged by the investigators in the present study. As a result, bilastine treatments significantly increased the ratio of improved patients (markedly improved plus moderately improved) than did placebo (Fig. 4). In other H_1-antihistamines in double-blind, placebo-controlled comparative trials in Japanese patients with CSU, the percentages of patients evaluated by the investigator as improved at the final assessment were 80.5% (loratadine, 10 mg, once a day),[16] 77.7% (olopatadine hydrochloride, 5 mg, twice a day),[22] and 69.1% (bepotastine besilate, 10 mg, twice a day).[23] The overall improvement of bilastine treatments, 74.7% (20 mg) and 84.8% (10 mg), indicates that the clinical efficacy of bilastine for the overall improvement is similar to that for other H_1-antihistamines. Furthermore, Zuberbier *et al.*[17] reported that bilastine 20 mg once daily significantly improved the TSS change from baseline at 4 weeks than did placebo, and it was comparable to levocetirizine hydrochloride 5 mg in a randomized, double-blind, placebo-controlled comparative phase III study in patients with chronic idiopathic urticaria (CSU).

Concerning the safety of the bilastine treatments, no serious AEs were reported in this study. There was no difference in the incidence of AEs between bilastine and placebo, and between different doses of bilastine in the treatments. A small population of the patients in bilastine groups developed nervous system disorders, the class effect AEs of H_1-antihistamines. However, the incidences were comparable to those in the placebo group. No other noteworthy drug-related AEs was observed, as compared with those reported overseas.[24] Thus, bilastine 20 and 10 mg showed a favorable safety profile in Japanese patients with CSU.

Meanwhile, the present study was conducted within a limited administration period of 2 weeks; the period of drug therapy for CSU is longer in actual clinical settings.[4] Therefore, future studies are needed to examine the safety and efficacy of long-term administration of bilastine to patients with CSU. During the same period of this study, a long-term administration study of bilastine in Japanese patients with CSU or pruritus accompanied by skin diseases was conducted, and the results of this study are awaited.

Differences between bilastine groups and placebo group in the daily TSS, itch score, rash score (Fig. 2) or DLQI scores (Fig. 3) among secondary efficacy endpoints were analyzed by the t-test according to the protocol approved the ethics committee. The same significance of differences was proved by the Bonferroni's multiple comparison tests as well.

In conclusion, 2-week treatment with bilastine at doses of 20 and 10 mg once a day was effective and tolerable in Japanese patients with CSU. Moreover, the efficacy of bilastine exhibited early onset of action, as evidenced by the relief of CSU symptoms by bilastine treatment at 1 day after the administration. These results confirm that bilastine is a safe and effective treatment for the management of Japanese patients with CSU.

Acknowledgments

We thank the study investigators and assistants at the investigative sites as shown below: 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), Noboru Murakami (Murakami Dermatology Clinic), Tomoko Matsuda (Matsuda Tomoko Dermatological Clinic), Keizo Matsuo (Matsuo Clinic), Tetsuo Matsuda (Matsuda Dermatology Clinic), Akito Toshitani (Toshitani Dermatology Clinic), Masahiro Kusuhara (Kusuhara Dermatology Clinic), Aisaku Yamamoto (Kosugi Dermatology Clinic), Taizo Hamaguchi (Hamaguchi Skin Clinic), Ryuji Maruyama (Maruyama Dermatology Clinic), Hiroto Kitahara (Kitahara Dermatology Clinic), Hiroe Kiryu (Kiryu Dermatology Clinic), Tomoki Okuda (Okuda Dermatology Clinic), Masaru Igarashi (Igarashi Dermatology Clinic), Sumio Oura (Soken Dermatology Clinic), Shuhei Fukuro (Fukuro Dermatology Clinic), Yoshiko Ito (Ito Dermatology Clinic), Mitsuru Iwata (Iwata Dermatology Clinic), Nobuaki Morishita (MIU Skin Clinic), Osamu Takeda (Takeda Dermatological Skin Care Clinic), Hiroko Koizumi (Koizumi Dermatology Clinic), Akira Eguchi (Eguchi Dermatology Clinic), Kenji Tashiro (Tashiro Dermatology Clinic), Fumihiro Kato (Kato Dermatology Clinic), Tomohiko Matsuyama (Matsuyama

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Dermatology Clinic), Akitoshi Hatamoto (Hatamoto Dermatology Clinic), Naoko Hattori (Naoko Dermatology Clinic), Shinsuke Tajiri (Tajiri Dermatology Clinic), Kenichi Tsutsui (Tsutsui Dermatology and Plastic Surgery Clinic), Akihiro Sasase (Sasase Dermatology Clinic), Seiki Sakaki (Sakaki Clinic of Dermatology and Surgery), Takeshi Yoshikawa (Yoshikawa Dermatology Clinic), Yukiko Kurikawa (Zoshiki Dermatology Clinic), Akio Taneda (Taneda Dermatology Clinic), Yuri Egawa (Yokohama Sotetsu Bldg. Dermatology and Urology Clinic), Akira Yoshioka (Yoshioka Dermatology Clinic), Yasushi Goto (Goto 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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.08.004.

Conflict of interest

MH received lecture and/or consultation fees from Taiho Pharmaceutical, Novartis, MSD, Teikoku Seiyaku and Mitsubishi Tanabe Pharma Co. MT and AS are employees of Taiho Pharmaceutical. AY and MF have no conflict of interest to declare.

Authors' contributions

MH, AY, and MF were medical advisers and provided suggestions on the study design, conduct of the study, and interpretation of data. MT and AS contributed to the study concept and design, the conduct of the study, and data analysis and interpretation. All authors listed were involved in the critical review and revision of the manuscript, and all provided final approval of the content.

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Supplementary Table 1

Grading score of rash

Score	Flare	Wheal	Synthetic score
0	Absent	Absent	No rash
1	Slight redness	Small swelling	Does not look too bad
2	Clear redness	Clear swelling	Looks bad
3	Strong redness	Remarkable swelling	Looks very bad

Supplementary Table 2

Grading score of itch

Score	Daytime	Nighttime
0	Virtually no itching	Virtually no itching
1	Occasionally feel itchy but not enough to scratch	Can fall asleep without scratching
2	Occasional itching and scratching	Can fall asleep but need to scratch
3	Considerable itching and scratching	Sometimes wake up because of itching
4	Cannot relax because of constant Itching	Cannot sleep because of itching

Supplementary Table 3

Assessment of overall improvement by the investigators

Score	Degree of rash
1. Markedly improved	Both itching and rash had disappeared. or Itching had disappeared and rash had improved significantly.
2. Moderately improved	Both itching and rash had improved greatly.
3. Mildly improved	Both itching and rash had improved a little.
4. No change	No change to itching and rash.
5. Exacerbated	Both itching and rash had worsened.