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Original Article

Efficacy and safety of bilastine in reducing pruritus in patients with chronic spontaneous urticaria and other skin diseases: an exploratory study

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ABSTRACT

Purpose: To evaluate the efficacy/safety of bilastine in pruritus relief in patients with chronic spontaneous urticaria (CSU) or other pruritic skin diseases.

Methods: In this multicenter, open-label, exploratory study (EudraCT No.: 2016-001505-17), 115 adults with CSU (n = 34), eczema/dermatitis (n = 30), prurigo (n = 25) or cutaneous pruritus (n = 26), received bilastine 20 mg once daily for 8 weeks, or in non-responder patients (<30% improvement in pruritus score at week 2), 40 mg/day from week 2.

Results: The mean change in weekly pruritus severity score from baseline to week 8 (primary endpoint) was reduced with bilastine (overall and by disease group); overall, percentage and absolute reductions were 71.16% and 1.63 points, respectively ($p < 0.001$). Updosed non-responders (n = 31) had improved weekly pruritus severity scores from baseline to week 8; percentage and absolute reductions were 49.08% and 1.13 points, respectively ($p < 0.001$). Bilastine improved the Dermatology Life Quality Index at weeks 4 and 8 ($p < 0.001$) in all disease groups, and the 7-day Urticaria Activity Score in CSU patients ($p < 0.001$). Bilastine was well tolerated.

Conclusions: Bilastine relieved pruritus associated with urticaria and other skin diseases, with a very good safety profile.

Keywords: bilastine, chronic spontaneous urticaria, pruritus, skin diseases, updosing

Introduction

Pruritus (itch) is a common symptom associated with a range of skin diseases, including urticaria, atopic dermatitis, eczema and prurigo (1–3). The presence of pruritus can have a significant impact on the quality of life (QoL) and psychosocial wellbeing of patients with skin diseases (4).

Urticaria is a mast cell-driven disease characterized by the development of wheals and/or angioedema; the pathophysiology of urticaria involves the release of histamine and other mediators from activated skin mast cells (3). Chronic urticaria is broadly classified into two subtypes - chronic spontaneous urticaria (CSU) and inducible urticaria. CSU is defined as the spontaneous appearance of wheals and/or angioedema for 6 or more weeks due to known or unknown causes (3). Current consensus guidelines recommend second-generation H₁-antihistamines for the first-line treatment of urticaria (3).

Bilastine is a potent and specific H₁-antihistamine with demonstrable efficacy for the symptomatic treatment of CSU. Treatment with bilastine 20 mg for 28 days significantly reduced symptoms of pruritus and wheals and improved patient QoL (5). Bilastine 20 mg also significantly reduced histamine-induced wheal and flare responses in healthy volunteers (6–8), with a more rapid onset of action than cetirizine 10 mg (6), desloratadine 5 mg and rupatadine 10 mg (8), and superiority over desloratadine and rupatadine for inhibiting wheal and flare responses, and itching sensation (8). A multicenter, open-label, phase III study also demonstrated the long-term efficacy, particularly in reducing pruritus, and safety of bilastine 20 mg in Japanese patients with CSU or pruritus associated with skin diseases (9). Moreover, the excellent efficacy and safety profile of bilastine make it the ideal H₁-antihistamine for

up dosing the daily dose four-fold in difficult-to-treat urticaria (10), as recommended by current EAACI/GA²LEN/EDF/WAO guidelines for the management of urticaria (3).

The main objective of the current study was to evaluate the efficacy of bilastine in the relief of pruritus in patients with CSU or other pruritic skin diseases. In addition to the assessment of efficacy outcomes in these disease groups, the effect of bilastine on patients' QoL, and the safety and tolerability of bilastine, were evaluated.

Patients and methods

This was a multicenter, open-label, phase IV study of the efficacy and safety of bilastine for the relief of pruritus in patients with CSU or other pruritic skin diseases, conducted at 10 European centers in Spain (2), Hungary (3) and Poland (5) [EudraCT No.: 2016-001505-17].

Inclusion and exclusion criteria

Main inclusion criteria were patients aged between 18 and 74 years diagnosed with CSU, eczema/dermatitis, prurigo, or cutaneous pruritus, who had not responded to placebo during the run-in period of 7 to 14 days and with at least 4 points for the sum of the itch score during the last 3 days of the run-in period. In addition, patients diagnosed with CSU were required to have ≥ 16 points for weekly Urticaria Activity Score (UAS7: sum of the daily UAS scores over 7 days) before enrolment. UAS is scored on a scale of 0 (absent) to 3 (intense) and is the sum of daily wheals and itch scores (3). The maximum UAS value is 6; the maximum UAS7 value is 42.

Patients included in the eczema/dermatitis group were diagnosed with acute, chronic, nummular, dyshidrotic, or asteatotic eczema; or contact, atopic or auto sensitization

dermatitis; or lichen simplex chronicus. Prurigo was diagnosed as acute, subacute or chronic disease; and cutaneous pruritus as systemic or localized disease.

Main exclusion criteria included: patients with, or with a history of, malignant tumors, or patients with severe concomitant diseases including diseases of the liver, kidney, thyroid, and heart, hematological diseases (e.g. pancytopenia, leukopenia), psychiatric/neurological disorders and autoimmune diseases; patients with fungal, bacterial or viral skin infections (excluding those not interfering with the efficacy evaluation); patients with a history of non-responsiveness or allergy to antihistamines; and patients with diseases that might interfere with efficacy evaluation: cholinergic, physical, paraneoplastic, parasitic, or pigmented urticaria, angiitis or collagen disease induced urticaria, severe dermographism, Schnitzler syndrome, cryopyrin associated periodic syndrome, and psoriasis; pregnant women, nursing mothers, and patients not using a reliable method of contraception. Patients who were treated with antihistamine, anti-allergic, antipruritic or anti-plasmin drugs, glycyrrhizinate or diaminodiphenyl sulfone within 7 days of enrolment; or with systemic corticosteroids, immunological drugs (e.g. methotrexate, cyclophosphamide), P-glycoprotein inhibitors, or tacrolimus hydrate within 30 days prior to enrolment, were also excluded.

Treatment

Patients were treated with oral bilastine 20 mg once daily for 8 weeks. Patients who failed to achieve at least a 30% improvement in pruritus score compared to baseline at week 2 were defined as non-responders. Non-responding patients received a dose increment of bilastine up to 40 mg daily (two 20 mg tablets) for the remaining 6 weeks of the study.

Study outcomes

The primary outcome was the mean change in weekly pruritus severity score (ranging from 0 [absent] to 3 [intense]) from baseline to week 8.

Secondary efficacy outcomes for CSU patients were mean change in weekly UAS7 from baseline to weeks 1, 2, 4 and 8; mean change in weekly pruritus severity score from baseline to weeks 1, 2 and 4; mean change in weekly visual analog scale (VAS) score for pruritus (from 0 to 100 mm) from baseline to weeks 1, 2, 4 and 8; change from baseline in daily UAS, daily wheal and itch, and daily itch; and change in Dermatology Life Quality Index (DLQI) (11) from baseline to weeks 4 and 8.

Secondary efficacy outcomes for patients with eczema/dermatitis, prurigo and cutaneous pruritus were mean change in weekly pruritus severity score from baseline to weeks 1, 2 and 4; mean change in weekly VAS score for pruritus from baseline to weeks 1, 2, 4 and 8; change in daily itch score from baseline; change in investigator's rash score (on a scale of 0 [absent] to 4 [severe]) from baseline to weeks 2, 4 and 8; change in DLQI from baseline to weeks 4 and 8; and for patients with eczema/dermatitis or prurigo, investigator-assessed general improvement factor of rash (on a scale of 1–6) at weeks 2, 4 and 8.

Safety outcomes were the incidence of adverse events (AEs), serious AEs (SAEs), and related AEs; and changes in clinical laboratory test results, electrocardiogram (ECG) and vital signs.

Statistical methods

The Full Analysis Set (FAS) population was used for the main analysis with the Per Protocol (PP) population used for complementary analysis for the primary endpoint.

All baseline scores were assessed as the mean of scores on the enrolment day and the previous 3 days (4 days in total), except for UAS7 which was the sum of the last 7 assessments before enrolment. For assessments performed only on planned visits, baseline values were taken at the enrolment visit.

The Safety Population comprised all patients who had received at least one dose of bilastine.

The primary endpoint, the mean change in weekly pruritus severity score (mean score at week 8 – mean baseline score), was analyzed with a paired two-sided Student's t-test with $\alpha = 0.05$, including its corresponding 95% confidence interval (CI). The non-parametric Wilcoxon test for paired data was used for non-normally distributed data. All analyses were performed by disease groups, without any formal comparisons between them. Similar analyses were carried out for secondary efficacy endpoints.

AEs and SAEs were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and their corresponding incidences were summarized as overall results, related events, and events by intensity. ECG, vital signs and laboratory data were displayed in terms of individual listings.

Ethical statement

This study was performed in strict compliance with ICHP-GCP Guidelines, the Declaration of Helsinki (18th World Medical Assembly, 1964) and its last revision (Fortaleza, October 2013), and local laws and regulations of the country where the study was performed. All patients provided written informed consent.

Results

Patient demographics

A total of 115 patients who were diagnosed with CSU ($n = 34$), eczema/dermatitis ($n = 30$), prurigo ($n = 25$) or cutaneous pruritus ($n = 26$), were included in the study (Figure 1). The eczema/dermatitis group comprised 19 patients diagnosed with atopic dermatitis, 7 with contact dermatitis, and 4 with chronic eczema. In the prurigo group, 24 patients were diagnosed with chronic prurigo, and 1 with subacute prurigo; and in the cutaneous pruritus group, 24 patients were diagnosed with systemic cutaneous pruritus, and 2 patients with localized cutaneous pruritus.

Demographic characteristics of patients at baseline are summarized in Table 1. Overall, there were more female ($n = 86$; 74.8%) than male ($n = 29$; 25.2%) participants. The mean age of patients was 42.83 years with a standard deviation (SD) of 14.58. The majority (93.9%) were within the 18–65 years age group.

Median time since diagnosis for all patients was 2 years (range: 0–45 years), which varied from 1 year (range 0–26 years) in the CSU group, to 2.5 years (range 0–45 years) in the eczema/dermatitis group.

Overall, 81 (70.4%) patients reported at least one concomitant medical condition (Table 1).

The most frequently reported conditions were allergic rhinitis in 26 (22.6%) patients, followed by asthma in 22 (19.1%), hypertension in 19 (16.5%), and allergic conjunctivitis in 15 (13.0%) patients.

A total of 87 (75.7%) patients reported taking at least one concomitant medication (Table 1).

The most frequently reported concomitant medications were emollients and protectives in 23 (20.0%) patients, followed by salbutamol in 16 (13.9%), soft soap in 12 (10.4%), paracetamol in 10 (8.7%), and levothyroxine sodium in 10 (8.7%) patients.

Treatment adherence was 100%.

Efficacy analyses

Primary endpoint

Analysis of all patients in the FAS population ($n = 111$) showed that bilastine produced a statistically significant reduction ($p < 0.001$) in the primary outcome, the mean change in weekly pruritus severity score from baseline to week 8 (Figure 2). The percentage reduction was 71.16% and the absolute reduction was 1.63 points for all patients. Bilastine also produced significant reductions in each disease group ($p < 0.001$ for all) with high rates of change in the CSU (85.43% and 2.11 points) and cutaneous pruritus groups (77.69% and 1.66 points); and lower rates in prurigo (60.06% and 1.30 points) and eczema/dermatitis (59.63% and 1.36 points) groups. Mean weekly pruritus severity scores at baseline and at week 8 in each disease group are shown in Figure 2. The primary outcome measure was also significant ($p < 0.001$) in the PP population ($n = 94$).

Ad-hoc analysis by responder patients in the PP population (n = 63), who achieved symptom relief $\geq 30\%$ at week 2, showed similar results to the FAS population: the mean reduction in weekly pruritus severity score from baseline to week 8 was significant in all patients, and in each patient group ($p < 0.001$ for all analyses) (Table 2). Non-responder patients (n = 31), who were defined at week 2 as having $< 30\%$ improvement in their pruritic score and were consequently updosed to bilastine 40 mg/day from week 2, showed a statistically significant improvement ($p < 0.001$) in weekly pruritus severity score from baseline to week 8. The percentage reduction was 49.08% and the absolute reduction was 1.13 points (Table 2).

There was a progressive reduction in weekly pruritus severity score during the course of the study (Figure 3).

Secondary endpoints

Bilastine produced a statistically significant improvement in the weekly pruritus severity score from baseline at weeks 1, 2 and 4 ($p < 0.001$ for all visits). The percentage reduction was 29.78% and the absolute mean reduction was 0.68 points at week 1; with further improvement to 43.73% and 1.02 points at week 2; and 65.28% and 1.51 points at week 4. By disease groups, the highest rates of pruritus relief were also found for the CSU group (40.20%, 56.40% and 77.64% at weeks 1, 2 and 4, respectively) and in the cutaneous pruritus group (30.39%, 46.47% and 74.94% at weeks 1, 2 and 4, respectively) (Table 3).

The change from baseline in the weekly pruritus severity score at weeks 1, 2 and 4, for responders and non-responders in the PP population, are shown in Table 4. The responder patient subgroup showed similar results to the FAS population. For the non-responder subgroup (Table 4), although there was no statistically significant difference at week 2 ($p =$

0.2162), the mean change from baseline in the weekly pruritus severity score at weeks 4 and 8 was statistically significant ($p < 0.001$ for each), after patients were up dosed with bilastine up to 40 mg/day. The percentage reduction for all patients at weeks 4 and 8 was 45.39% and 49.08%, respectively, with absolute reductions of 1.05 and 1.13 points, respectively.

Bilastine also produced a statistically significant reduction in the pruritus VAS score in all patients from baseline to weeks 1, 2, 4 and 8 ($p < 0.001$ for all). There was a progressive reduction in this parameter (Figure 4), with percentage and absolute mean reductions of 77.48% and 44.96 mm, respectively, at week 8. The pruritus VAS scores were reduced significantly from baseline to weeks 1, 2, 4 and 8 in each disease group ($p < 0.001$; except week 1 in the eczema/dermatitis group, $p = 0.0015$). By disease groups, the CSU group showed the highest reductions (52.91%, 66.86%, 88.14%, and 92.59%, at weeks 1, 2, 4 and 8, respectively), followed by cutaneous pruritus (18.65%, 46.71%, 75.12%, and 83.21%, respectively).

In CSU patients, daily UAS was improved significantly following a single day's treatment with bilastine. Absolute mean reduction in daily UAS was 1.52 points ($p < 0.001$). Evaluation of UAS7 scores in the overall CSU group showed that bilastine produced significant reductions from baseline, after 1, 2, 4 and 8 weeks (all $p < 0.001$). There was a progressive improvement in UAS7 scores with percentage reductions of 32.10% (absolute mean reduction, 9.84 points), 51.84% (15.87 points), 74.84% (22.90 points), and 82.74% (25.65 points) after 1, 2, 4 and 8 weeks, respectively. Similar results were obtained in the responder and, from week 2, non-responder subgroups (Figure 5).

Bilastine produced a statistically significant decrease in the DLQI for all patients and in each patient group at weeks 4 and 8 ($p < 0.001$ for all; Table 5, Figure 6). All patients showed a general decrease in the DLQI with statistically significant reductions in the overall score for both week 4 (percentage reduction 61.41%, absolute mean reduction 8.23 points) and week 8 (75.96%, 9.82 points) with respect to the baseline assessment in the FAS population ($p < 0.001$). By disease groups, these differences were also statistically significant ($p < 0.001$ for each group at weeks 4 and 8), with reductions in DLQI in CSU patients at week 4 of 73.02% (10.10 points) and week 8 of 89.62% (12.10 points); in eczema/dermatitis patients at week 4 of 44.42% (6.24 points) and week 8 of 66.76% (8.48 points); in the prurigo group, these reductions were 47.06% (6.52 points) and 63.58% (8.12 points) at weeks 4 and 8, respectively; and in the cutaneous pruritus group, these changes were 80.31% (9.88 points) and 81.86% (10.23 points), respectively.

Two efficacy outcomes, the investigator's rash score and general improvement, were evaluated only in the eczema/dermatitis and prurigo groups. In an analysis of both groups combined ($n = 54$), bilastine produced a significant improvement in investigator's rash score from baseline at weeks 4 and 8 ($p < 0.001$ for each). This was attributable to significant reductions in the prurigo group, with mean reductions in rash score at weeks 4 and 8 of 1.04 and 1.36, respectively. No significant improvement in rash score was found in the eczema/dermatitis group. General improvement was shown in the combined eczema/dermatitis and prurigo groups from week 2 of bilastine administration, with 66.7% (36/54), 79.6% (43/54) and 87.0% (47/54) of patients reporting any improvement (mild, moderate or marked) at weeks 2, 4 and 8, respectively.

Safety analyses

During the study, 92 treatment emergent AEs (TEAEs) were reported in 39 (33.9%) patients included in the study, after administration of bilastine. By treatment group: 10 (29.4%) patients with CSU reported 16 TEAEs; 10 (33.3%) patients with eczema/dermatitis reported 39 TEAEs; 12 (48.0%) patients with prurigo reported 22 TEAEs; and 7 (26.9%) patients with cutaneous pruritus reported 15 TEAEs. The most frequently reported TEAEs were headache (reported 20 times in 8 [7.0%] patients) and nasopharyngitis (reported 8 times in 8 [7.0%] patients). All TEAEs were mild (49 of 92 reported events) or moderate (43 of 92 reported events) in intensity.

Five of the 92 TEAEs (5.4%) were considered by the investigators to be possibly drug-related, and all were experienced by a single patient in the eczema/dermatitis group. These TEAEs were palpitations, dry mouth, decreased appetite, hypoesthesia and insomnia. All were mild in intensity and no remedial therapy was required.

No SAEs were observed during the study.

The vast majority of laboratory values were within normal ranges, with deviations from reference ranges being relatively minor and not resulting in study discontinuation for any patient. None of the abnormalities were considered related to bilastine treatment. Two AEs included abnormal blood creatine phosphokinase (CPK) levels which were mild in intensity. CPK levels recovered or were recovering at the end of the study without the need for any remedial therapy.

Discussion

This clinical trial was designed as an exploratory, international, multicenter study to evaluate the efficacy of bilastine 20 mg once daily for 8 weeks (or bilastine 40 mg/day from week 2 if the patient was a non-responder) in the relief of pruritus associated with urticaria (CSU) and other skin diseases (eczema/dermatitis, prurigo and cutaneous pruritus) in adults.

Treatment with bilastine for 8 weeks produced a statistically significant improvement in the primary efficacy endpoint – change in the weekly pruritus severity score from baseline, in all patients and in each patient group. The improvement of pruritus severity at 8 weeks was supported by results at weeks 1, 2 and 4, which also showed highly significant reductions from baseline. Furthermore, VAS for pruritus showed the same reduction profile and statistically significant improvements from weeks 1 to 8, with the highest rates found in the CSU group followed by the cutaneous pruritus group. In the CSU group, significant improvements in UAS7 were also found at weeks 1, 2, 4 and 8.

These results are similar to those found in a recent study performed in Japanese patients with the same disease groups (9), which reported significant improvement in changes in itch score from baseline, following treatment with bilastine 20 mg for 52 weeks. Significantly decreased itch scores were demonstrable at 2 weeks and efficacy was maintained throughout the study. Similarly, in CSU patients, the combined efficacy outcome of rash and itch was improved significantly from week 2, and for the duration of the study (9). Thus, improvement in symptoms in CSU and other skin diseases occurs within the first 2 weeks of bilastine therapy. These results are in line with those from another recently published study of bilastine in patients with CSU, which reported a significant improvement in the combined efficacy

outcome of rash and itch following 1 day of treatment, and which was maintained for the duration of the study (12).

In the current exploratory study, an additional *ad-hoc* analysis was performed for responder and non-responder patients who were defined based on achievement or failure of an improvement in pruritus severity score of $\geq 30\%$ at week 2. Responder patients showed similar efficacy results to all patients. Although weekly pruritus severity score was not significantly different from baseline at week 2 in non-responders, following up dosing at week 2 to bilastine 40 mg/day, non-responder patients showed statistically significant improvement in their weekly pruritus severity score at weeks 4 and 8, which demonstrates the effectiveness of this strategy. Urticaria guidelines recommend a trial of up dosing (up to four-fold) for modern second-generation H₁-antihistamines in patients with inadequate control after 2–4 weeks or earlier using standard doses (3). Up dosing with bilastine (to 40 mg or 80 mg) has been shown to be effective and safe in CSU patients who had previously failed treatment with a second-generation H₁-antihistamine, other than bilastine, at the licensed dose (13). In patients with cold contact urticaria, up dosing to bilastine 80 mg was safe and effective in reducing symptoms (14).

All disease groups treated with bilastine showed significant improvement in QoL at weeks 4 and 8. The mean reduction in DLQI score at week 8 for all patients was 9.82. These results are clinically relevant as Shikhar et al. recommended a minimal important difference for a change in the DLQI total score between 2.24 and 3.1 for patients with chronic idiopathic urticaria (15). DLQI changes in each patient group were also clinically relevant with reductions in DLQI scores ranging from 12.10 for CSU patients to 8.12 in the prurigo group. In common with these results, two recent studies of bilastine, one in CSU and pruritus-

associated skin diseases (9), and the other in CSU patients (12), also demonstrated that bilastine produced significant improvements in QoL assessed by total DLQI.

The safety profile of bilastine was good with a low rate of TEAEs (in 33.9% of patients). The most frequent TEAEs reported during the study were headache (20 events in 8 patients [7.0%]) and nasopharyngitis (8 events in 8 patients [7.0%]), which were mild to moderate in intensity. No episodes of somnolence were reported during the study, interesting data considering that 31 patients were treated with bilastine 40 mg during 6 weeks. Five TEAEs, all reported in a single patient, were considered to be drug-related, and were mild in intensity. These results are in line with the known safety profile of bilastine which is very similar to that of placebo, and with insignificant adverse effects on the central nervous system (16,17). The long-term (52-week) study of bilastine for patients with CSU and related skin diseases emphasized the good safety profile of the drug. AEs were reported in 64.5% of patients, including seven patients (3.6%) with headache. Bilastine-related AEs were reported in 2.5% of patients (5/197), including somnolence in two patients (1.0%) (9).

In conclusion, bilastine has demonstrated efficacy for the relief of pruritus associated with urticaria and other skin diseases in adults, with a very good safety profile. These exploratory findings pave the way for future studies with bilastine which could include the treatment of patients with pruritus, independent of baseline condition. Moreover, the *ad-hoc* analysis showed that bilastine up dosing to 40 mg (double dose), for those patients who do not achieve a significant improvement after 2 weeks of treatment, is efficacious without any safety concerns and this also warrants further exploration in future clinical studies.

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Disclosure statement

Bernadetta Majorek-Olechowska and Esther Serra-Baldrich have not declared conflict of interest.

Zoltan Novak has been member of the advisory boards of different pharmaceutical companies: AstraZeneca, GlaxoSmithKline, BerlinChemie and also usually gives lectures for the same companies

Cristina Campo, Aintzane García-Bea, and Luis Labeaga are full-time employees of FAES FARMA S. A.

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Figure legends

Figure 1. Disposition of patients. CSU: chronic spontaneous urticaria; FAS: Full Analysis Set.

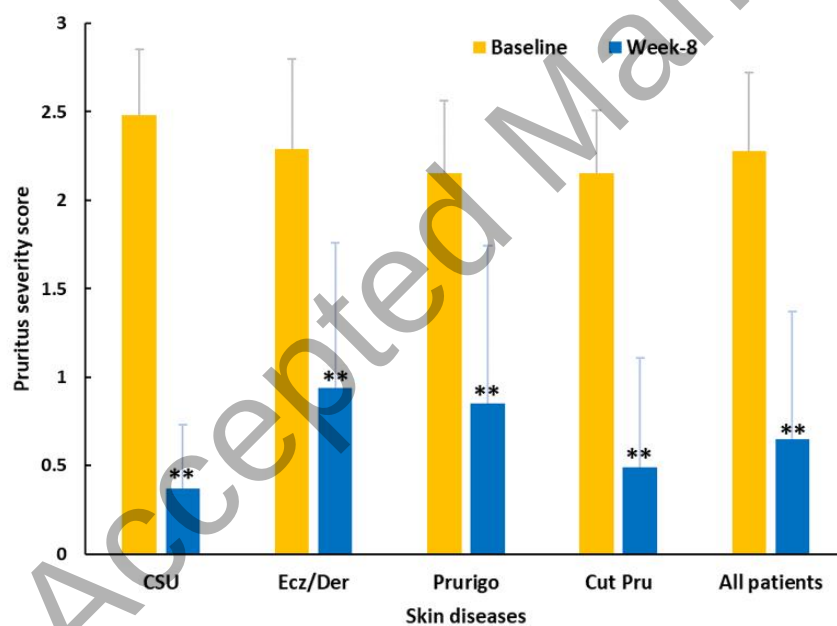
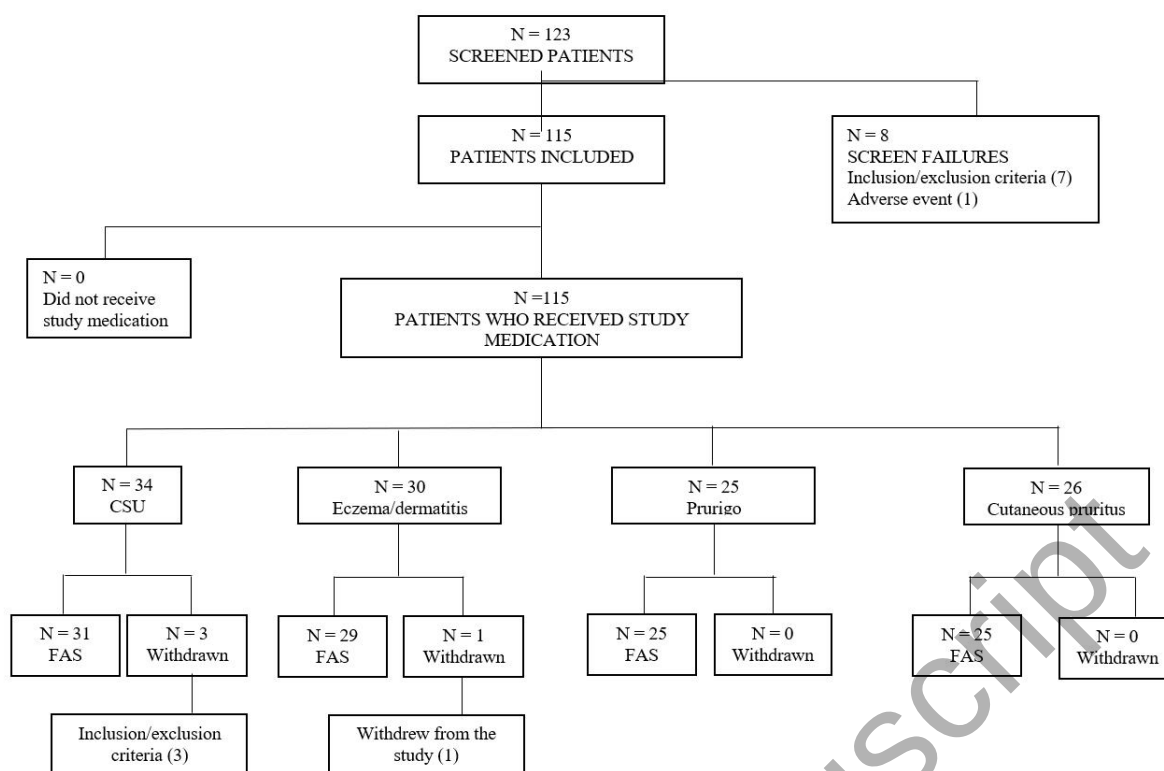
Figure 2. Pruritus severity scores at baseline and week 8 following bilastine treatment in chronic spontaneous urticaria (CSU, n = 31), eczema/dermatitis (Ecz/Der, n = 29), prurigo (n = 25), cutaneous pruritus (Cut Pru, n = 26), and all patients (n = 111, FAS population). ** $p < 0.001$ for comparison of baseline and week 8 scores for each treatment group.

Figure 3. Pruritus severity scores from baseline following bilastine treatment in chronic spontaneous urticaria (CSU, n = 31), eczema/dermatitis (Ecz/Der, n = 29), prurigo (n = 25), cutaneous pruritus (Cut Pru, n = 26), and all patients (n = 111, FAS population).

Figure 4. Visual analog scale (VAS) for pruritus scores from baseline following bilastine treatment in chronic spontaneous urticaria (CSU, n = 31), eczema/dermatitis (Ecz/Der, n = 29), prurigo (n = 25), cutaneous pruritus (Cut Pru, n = 26), and all patients (n = 111, FAS population).

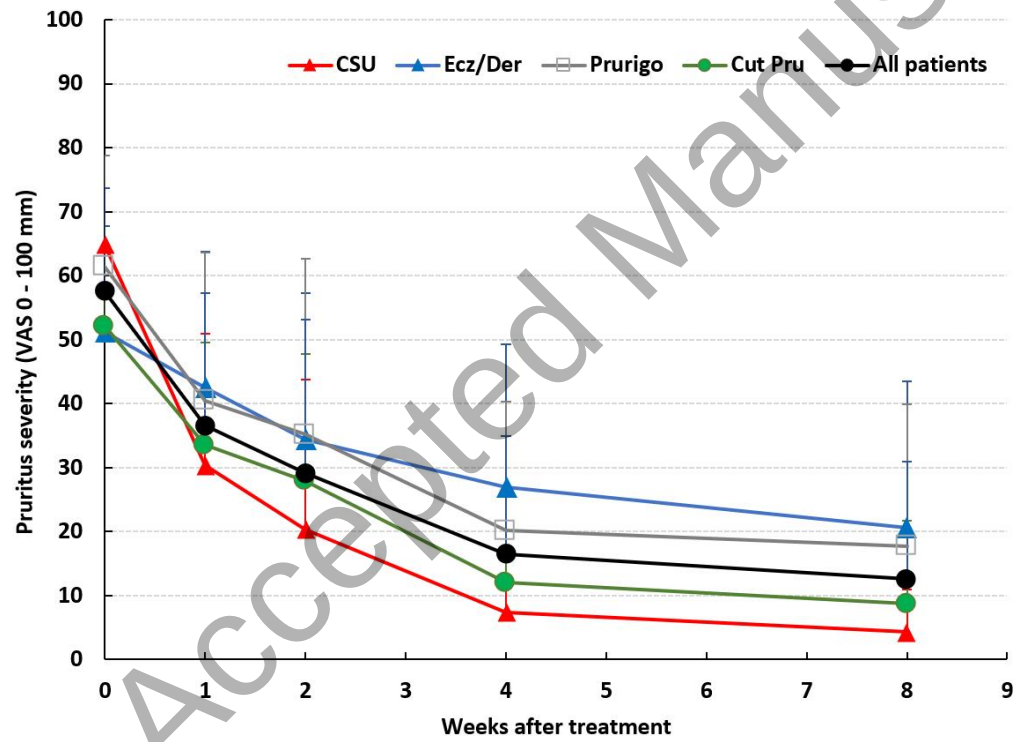
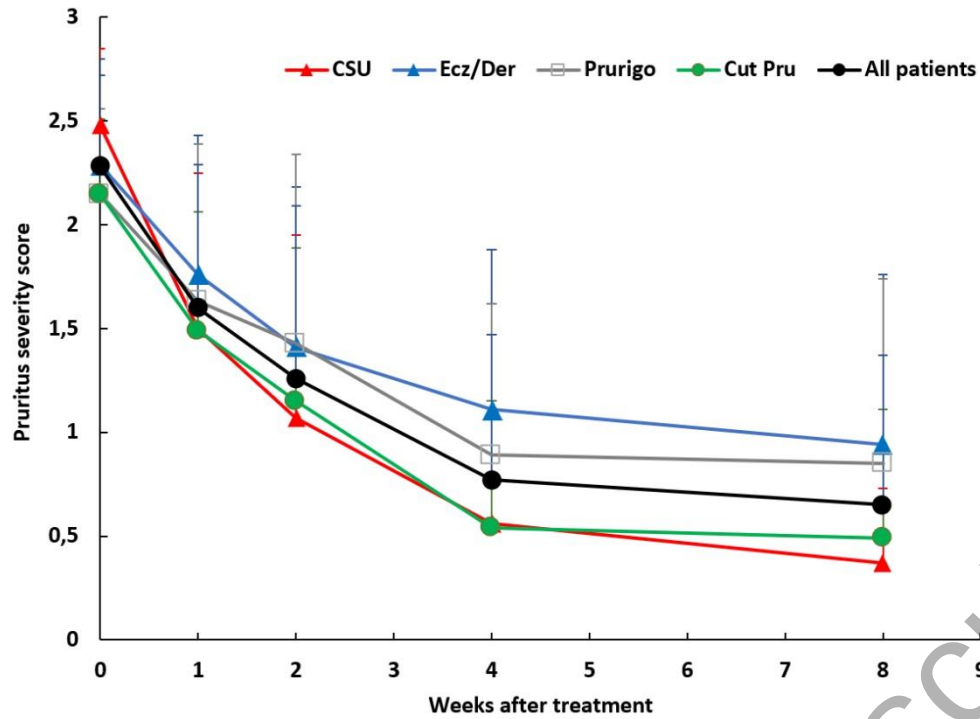
Figure 5. Reduction in weekly Urticaria Activity Score (UAS7) from baseline to Week 1, 2, 4 and 8 (PP population).

Figure 6. Reduction in Dermatology Life Quality Index (DLQI) scores from baseline to Week 4 and 8 (FAS population). ** $p < 0.001$ vs. baseline.



Weekly pruritus severity score	CSU (n=31)	Ecz/Der (n=29)	Prurigo (n=25)	Cut Pru (n=26)	All (n=111)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	2.48 (0.37)	2.29 (0.51)	2.15 (0.41)	2.15 (0.36)	2.28 (0.44)
Week 8	0.37 (0.36)	0.94 (0.82)	0.85 (0.89)	0.49 (0.62)	0.65 (0.72)
Reduction at Week 8	2.11 (0.44)	1.36 (0.79)	1.30 (0.92)	1.66 (0.63)	1.63 (0.72)
% reduction at Week 8	85.43 (13.66)	59.63 (32.96)	60.06 (39.19)	77.69 (25.43)	71.16 (30.66)
p-value	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 [*]

* Wilcoxon signed-rank test; ⁺ paired t-test.



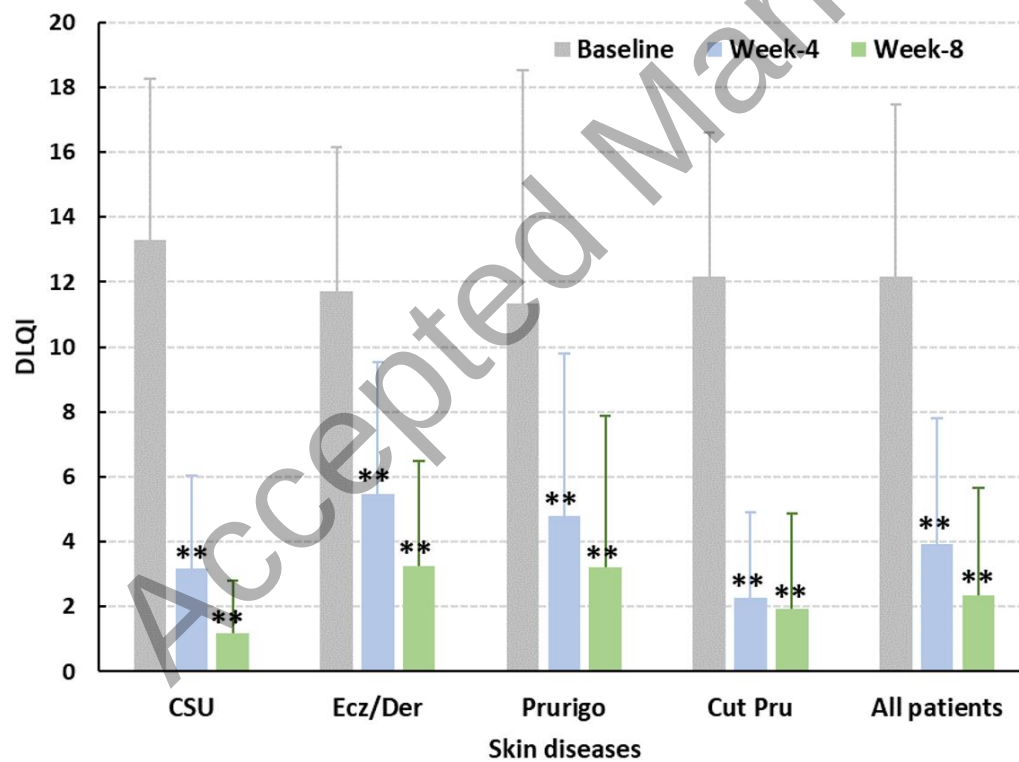
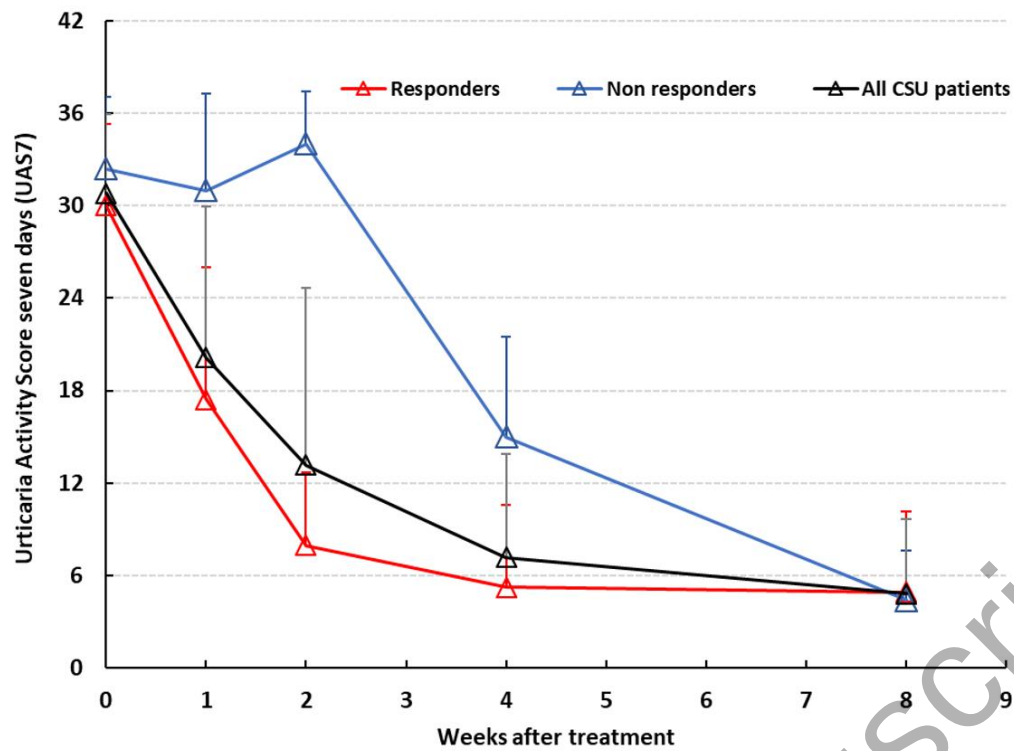


Table 1. Demographic characteristics of patients at baseline.

	Chronic spontaneous urticaria (CSU) (n = 34)	Eczema/dermatitis (n = 30)	Prurigo (n = 25)	Cutaneous pruritus (n = 26)	All (n = 115)
Gender Female/male: n (%)	27 (79.4%)/7 (20.6%)	18 (60.0%)/12 (40.0%)	20 (80.0%)/5 (20.0%)	21 (80.8%)/5 (19.2%)	86 (74.8%)/29 (25.2%)
Age: mean (SD) ≥18 to <65 years: n (%) ≥65 to ≤75 years: n (%)	43.85 (14.59) 33 (97.1%) 1 (2.9%)	37.30 (11.45) 30 (100.0%) 0 (0.0%)	46.68 (14.16) 23 (92.0%) 2 (8.0%)	44.19 (16.98) 22 (84.6%) 4 (15.4%)	42.83 (14.58) 108 (93.9%) 7 (6.1%)
Ethnic origin White/Caucasian: n (%) American Indian: n (%)	34 (100.0%) 0 (0.0%)	30 (100.0%) 0 (0.0%)	24 (96.0%) 1 (4.0%)	26 (100.0%) 0 (0.0%)	114 (99.1%) 1 (0.9%)
BMI (kg/m ²): mean (SD)	26.53 (6.08)	25.62 (3.91)	28.09 (5.04)	25.69 (4.59)	26.44 (5.05)
Concomitant medical condition(s): n (%)	28 (82.4%)	21 (70.0%)	18 (72.0%)	14 (53.8%)	81 (70.4%)
Concomitant medication(s): n (%)	27 (79.4%)	24 (80.0%)	20 (80.0%)	16 (61.5%)	87 (75.7%)

Table 2. Mean change in weekly pruritus severity score from baseline to Week 8: responder and non-responder analysis (PP population, N = 94).

Weekly pruritus severity score, mean (SD)	Responders				
	Chronic spontaneous urticaria (n = 20)	Eczema/dermatitis (n = 16)	Prurigo (n = 12)	Cutaneous pruritus (n = 15)	All (n = 63)
Baseline	2.45 (0.39)	2.20 (0.53)	2.19 (0.39)	2.12 (0.19)	2.26 (0.41)
Week 8	0.35 (0.35)	0.48 (0.45)	0.33 (0.41)	0.26 (0.35)	0.36 (0.39)
Reduction at Week 8	2.10 (0.46)	1.72 (0.65)	1.85 (0.59)	1.86 (0.37)	1.90 (0.53)
% reduction at Week 8	86.05 (13.96)	76.88 (23.22)	84.20 (19.31)	88.04 (16.42)	83.84 (18.32)
p-value	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺
	Non-responders				
	Chronic spontaneous urticaria (n = 5)	Eczema/dermatitis (n = 9)	Prurigo (n = 9)	Cutaneous pruritus (n = 8)	All (n = 31)
Baseline	2.45 (0.33)	2.39 (0.55)	2.31 (0.37)	2.22 (0.45)	2.33 (0.43)
Week 8	0.26 (0.12)	1.90 (0.57)	1.41 (1.16)	0.77 (0.66)	1.20 (0.96)
Reduction at Week 8	2.19 (0.38)	0.48 (0.31)	0.89 (1.08)	1.45 (0.70)	1.13 (0.91)
% reduction at Week 8	89.27 (5.09)	20.78 (13.70)	39.76 (48.63)	66.29 (25.46)	49.08 (38.08)
p-value	0.0625 [*]	0.0015 ⁺	0.0376 ⁺	0.0078 ⁺	<0.001 ⁺

* Wilcoxon signed-rank test; ⁺ paired t-test.

Table 3. Mean change in weekly pruritus severity score from baseline to Week 1, 2 and 4 (FAS population, N = 111).

Weekly pruritus severity score, mean (SD)	Chronic spontaneous urticaria (n = 31)	Eczema/dermatitis (n = 29)	Prurigo (n = 25)	Cutaneous pruritus (n = 26)	All (n = 111)
Baseline	2.48 (0.37)	2.29 (0.51)	2.15 (0.41)	2.15 (0.36)	2.28 (0.44)
Week 1	1.50 (0.75)	1.76 (0.67)	1.63 (0.76)	1.49 (0.57)	1.60 (0.69)
Reduction at Week 1	0.98 (0.68)	0.53 (0.49)	0.52 (0.76)	0.66 (0.51)	0.68 (0.64)
% reduction at week 1	40.20 (29.09)	23.73 (23.31)	23.25 (34.61)	30.39 (23.67)	29.78 (28.42)
p-value	<0.001 ⁺	<0.001 ⁺	<0.001 [*]	<0.001 [*]	<0.001 [*]
Week 2	1.07 (0.88)	1.41 (0.77)	1.43 (0.91)	1.15 (0.74)	1.26 (0.83)
Reduction at Week 2	1.40 (0.91)	0.88 (0.70)	0.72 (0.99)	1.00 (0.69)	1.02 (0.86)
% reduction at Week 2	56.40 (36.40)	38.89 (31.28)	30.80 (49.02)	46.47 (32.67)	43.73 (38.32)
p-value	<0.001 [*]	<0.001 ⁺	0.0013 ⁺	<0.001 ⁺	<0.001 ⁺
Week 4	0.56 (0.52)	1.11 (0.77)	0.89 (0.73)	0.54 (0.61)	0.77 (0.70)
Reduction at Week 4	1.92 (0.57)	1.18 (0.81)	1.26 (0.81)	1.62 (0.65)	1.51 (0.77)
% reduction at Week 4	77.64 (19.84)	50.00 (35.32)	57.64 (34.27)	74.94 (27.04)	65.28 (31.42)
p-value	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺

* Wilcoxon signed-rank test; ⁺ paired t-test.

Table 4. Mean change in weekly pruritus severity score from baseline to Week 1, 2 and 4: responder and non-responder analysis (PP population, N = 94).

Weekly pruritus severity score, mean (SD)	Responders				
	Chronic spontaneous urticaria (n = 20)	Eczema/dermatitis (n = 16)	Prurigo (n = 12)	Cutaneous pruritus (n = 15)	All (n = 63)
Baseline	2.45 (0.39)	2.20 (0.53)	2.19 (0.39)	2.12 (0.19)	2.26 (0.41)
Week 1	1.24 (0.69)	1.49 (0.68)	1.18 (0.75)	1.30 (0.58)	1.30 (0.67)
Reduction at Week 1	1.21 (0.57)	0.71 (0.51)	1.01 (0.80)	0.82 (0.58)	0.95 (0.62)
% reduction at Week 1	50.91 (24.98)	33.30 (24.68)	46.13 (34.96)	38.59 (26.99)	42.60 (27.77)
<i>p-value</i>	<0.001 ⁺	<0.001 ⁺	0.0011 ⁺	<0.001 ⁺	<0.001 [*]
Week 2	0.56 (0.40)	0.87 (0.43)	0.65 (0.50)	0.62 (0.39)	0.67 (0.43)
Reduction at Week 2	1.89 (0.48)	1.34 (0.42)	1.53 (0.65)	1.50 (0.40)	1.59 (0.52)
% reduction at Week 2	77.26 (17.27)	61.28 (14.47)	69.51 (23.63)	70.79 (17.99)	70.18 (18.73)
<i>p-value</i>	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺
Week 4	0.40 (0.42)	0.74 (0.60)	0.49 (0.47)	0.29 (0.31)	0.48 (0.48)
Reduction at Week 4	2.05 (0.47)	1.46 (0.86)	1.70 (0.62)	1.83 (0.35)	1.78 (0.63)
% reduction at Week 4	84.11 (15.90)	62.00 (38.88)	77.32 (22.09)	86.49 (15.42)	77.77 (26.06)
<i>p-value</i>	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 [*]	<0.001 [*]
	Non-responders				
	Chronic spontaneous urticaria (n = 5)	Eczema/dermatitis (n = 9)	Prurigo (n = 9)	Cutaneous pruritus (n = 8)	All (n = 31)
Baseline	2.45 (0.33)	2.39 (0.55)	2.31 (0.37)	2.22 (0.45)	2.33 (0.43)
Week 1	2.26 (0.57)	2.19 (0.56)	2.32 (0.28)	1.79 (0.41)	2.13 (0.48)
Reduction at Week 1	0.19 (0.50)	0.20 (0.38)	-0.01 (0.32)	0.43 (0.29)	0.20 (0.38)
% reduction at Week 1	7.81 (21.65)	7.44 (15.89)	-1.69 (13.79)	18.77 (12.70)	7.77 (16.65)
<i>p-value</i>	0.4385 ⁺	0.1536 ⁺	0.9152 ⁺	0.0037 ⁺	0.0076 ⁺
Week 2	2.51 (0.24)	2.33 (0.36)	2.33 (0.34)	1.93 (0.34)	2.26 (0.38)
Reduction at Week 2	-0.006 (0.17)	0.06 (0.28)	-0.03 (0.36)	0.29 (0.32)	0.07 (0.32)

% reduction at Week 2	-3.11 (6.92)	0.08 (13.23)	-2.27 (14.30)	11.98 (12.18)	1.96 (13.41)
p-value	0.4363 ⁺	0.5721 ⁺	0.8233 ⁺	0.0367 ⁺	0.2162 ⁺
Week 4	1.00 (0.40)	1.83 (0.59)	1.35 (0.87)	0.77 (0.69)	1.28 (0.78)
Reduction at Week 4	1.45 (0.61)	0.56 (0.25)	0.96 (0.90)	1.45 (0.76)	1.05 (0.75)
% reduction at Week 4	58.10 (18.29)	24.76 (11.85)	40.78 (39.52)	65.85 (29.03)	45.39 (31.11)
p-value	0.0062 ⁺	<0.001 ⁺	0.0128 ⁺	0.001 ⁺	<0.001 ⁺

* Wilcoxon signed-rank test; ⁺ paired t-test.

Table 5. Change in Dermatology Life Quality Index score from baseline to week 4 and 8 in the FAS population (N = 111).

	Chronic spontaneous urticaria (n = 31)	Eczema/dermatitis (n = 29)	Prurigo (n = 25)	Cutaneous pruritus (n = 26)	All (n = 111)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	13.29 (4.99)	11.72 (4.43)	11.32 (7.20)	12.15 (4.45)	12.17 (5.31)
Week 4	3.19 (2.83)	5.48 (4.06)	4.80 (5.00)	2.27 (2.63)	3.94 (3.88)
Change at Week 4	-10.10 (5.77)	-6.24 (6.10)	-6.52 (6.98)	-9.88 (5.00)	-8.23 (6.18)
% of change at Week 4	-73.02 (23.77)	-44.42 (54.91)	-47.06 (65.90)	-80.31 (21.21)	-61.41 (47.08)
p-value	<0.001 *	<0.001 ⁺	<0.001 ⁺	<0.001 *	<0.001 ⁺
Week 8	1.19 (1.62)	3.24 (3.26)	3.20 (4.67)	1.92 (2.95)	2.35 (3.31)
Change at Week 8	-12.10 (5.33)	-8.48 (5.02)	-8.12 (7.91)	-10.23 (5.58)	-9.82 (6.13)
% of change at Week 8	-89.62 (14.76)	-66.76 (35.56)	-63.58 (53.08)	-81.86 (26.13)	-75.96 (35.62)
p-value	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺	<0.001 ⁺

* Wilcoxon signed-rank test; ⁺ paired t-test.