ORIGINAL ARTICLE

Bilastine 0.6% Preservative-Free Eye Drops as an Effective Once-Daily Treatment for the Signs and Symptoms of Allergic Conjunctivitis: A Pooled Analysis of 2 Randomized Clinical Trials

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Abstract

Background: Allergic conjunctivitis is the most common type of ocular allergy.
Objective: The objective of this study was to evaluate the efficacy of a new once-daily, preservative-free, bilastine 0.6% eye drop formulation for the treatment of allergic conjunctivitis.
Methods: Two double-masked, vehicle-controlled, clinical studies (a phase 2 dose-ranging study and a phase 3 efficacy study) were conducted to assess the efficacy of bilastine ophthalmic solution for treatment of the signs and symptoms of allergic conjunctivitis. Both studies used the Ora-CAC® Conjunctival Allergen Challenge (CAC) model to enable observation of allergic responses under controlled conditions. Each study was analyzed separately and then combined to create an integrated data set.
Results: Efficacy was achieved for the primary efficacy endpoint of ocular itching with 3 bilastine concentrations (0.2%, 0.4%, and 0.6%) at 15 minutes and 8 hours after instillation. Bilastine 0.6% ophthalmic solution was also efficacious at 16 hours after instillation. Bilastine 0.6% ophthalmic solution demonstrated noninferiority to ketotifen 0.025% at the onset of action. According to the integrated data set, differences between vehicle and bilastine 0.6% after instillation were significant at all time points both at onset (15 minutes) and after a prolonged duration (16 hours).
Conclusion: This multitrial assessment suggests that bilastine 0.6% ophthalmic solution is efficacious for the treatment of the signs and symptoms of allergic conjunctivitis, with a rapid onset and prolonged duration of action, and has a favorable safety profile. The added convenience of once-daily dosing may contribute to adherence and improve quality of life.

Key words: Allergic conjunctivitis. Antihistamine. Bilastine. Preservative-free. Once-daily.

Resumen

Antecedentes: La conjuntivitis alérgica es el tipo más común de alergia ocular.
Objetivo: El objetivo de este estudio fue evaluar la eficacia de una nueva formulación oftálmica de bilastina 0,6%, de administración única diaria y sin conservantes, para el tratamiento de la conjuntivitis alérgica.
Métodos: Se realizaron dos estudios clínicos doble ciego, controlados por vehículo (un estudio de búsqueda de dosis de fase 2 y un estudio de eficacia de fase 3), para evaluar la eficacia de la solución oftálmica de bilastina para el tratamiento de los signos y síntomas de la conjuntivitis alérgica. Ambos estudios utilizaron el modelo de provocación conjuntival Ora-CAC® *Conjunctival Allergen Challenge*, para evaluar las respuestas alérgicas bajo condiciones controladas. Cada estudio se analizó por separado y luego se combinaron para crear un conjunto de datos integrado.
Resultados: Se logró el objetivo de eficacia para el criterio principal de valoración del prurito ocular para tres concentraciones de bilastina (0,2%, 0,4% y 0,6%) a los 15 minutos y 8 horas después del tratamiento. La solución oftálmica de bilastina al 0,6% también fue eficaz a las 16 horas después de su aplicación inicial. La solución oftálmica de bilastina al 0,6% demostró no ser inferior al ketotifeno 0,025% al inicio de la acción. A partir del conjunto de datos integrados, las diferencias entre el vehículo y bilastina al 0,6% fueron significativas en todos los tiempos analizados, tanto al inicio (15 minutos) como durante un tiempo prolongado (16 horas) después de su aplicación.
Conclusión: Esta evaluación de múltiples ensayos sugiere que la solución oftálmica de bilastina al 0,6% es eficaz para el tratamiento de los signos y síntomas de la conjuntivitis alérgica, con una acción rápida y de duración prolongada, y tiene un buen perfil de seguridad. La ventaja adicional de un régimen de dosificación de una vez al día puede contribuir a la adherencia del paciente al tratamiento y a mejorar su calidad de vida.

Palabras clave: Conjuntivitis alérgica. Antihistamínico. Bilastina. Sin preservantes. Una vez al día.

Summary box

- **What do we know about this topic?**
  Bilastine, a second-generation antihistamine, is approved for the treatment of allergic rhinoconjunctivitis and urticaria in its oral formulation. An ophthalmic formulation was developed for treatment of the signs and symptoms of allergic conjunctivitis. Its efficacy was evaluated here.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  This multitrial assessment shows that the newly developed once-daily and preservative-free ophthalmic formulation of bilastine 0.6% is efficacious for rapid reduction of ocular itching and safe in patients with allergic conjunctivitis. The once-daily dosing regimen may contribute to adherence.

Introduction

Allergic conjunctivitis is the most common type of ocular allergy (~80% to 90%), with a global prevalence ranging from 15% to 40% [1]. Approximately 50% of patients who seek treatment for allergies present with ocular symptoms [2]. Allergic conjunctivitis results from a predominantly IgE-mediated inflammatory reaction in the conjunctiva or an immediate hypersensitivity mechanism [3] and often coexists with other allergic diseases, such as asthma, allergic dermatitis, and food allergy, and particularly with allergic rhinitis [4]. Therefore, the term rhinoconjunctivitis is often used interchangeably to refer to both entities [5,6].

Given their faster onset of action, topical agents are preferred when symptoms are mainly ocular. Some oral antihistamines for allergic conjunctivitis result in adverse effects such as fatigue and somnolence [7,8], while other, less sedating oral treatments can result in dry eye [9]. Topical administration in the eye reduces the risk of fatigue and somnolence associated with oral administration owing to the lower systemic bioavailability of drugs administered via eye drops. Topical ophthalmic treatments often show superiority to oral and nasal treatments when local symptoms are predominant [10], and the European Academy of Allergy and Clinical Immunology (EAACI) recommends topical treatment for allergic conjunctivitis [11]. In addition, oral and topical administration of corticosteroids is associated with systemic adverse effects such as cataracts and elevated intraocular pressure [12]. Moreover, certain topical vasoconstrictor eye drops can also result in a rebound effect of ocular redness [13]. Therefore, novel therapeutic alternatives are needed.

Bilastine is a second-generation, nonsedating, selective antihistamine that was initially developed as an oral formulation for the treatment of allergic rhinoconjunctivitis and urticaria. It has a chemical structure similar to that of piperidinyl-benzimidazole but is not structurally derived from it. Similarly, it is not a metabolite or enantiomer of any of the existing antihistamines, but rather an original molecule. Bilastine is authorized worldwide (28 European countries and over 94 non-European countries) for the symptomatic treatment of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria in adults and adolescents. It has been shown to be effective in controlling the ocular signs and symptoms of allergic conjunctivitis [14].

Based on the demonstrated efficacy and safety of the oral formulation and the superiority of topical antihistamines over oral antihistamines for the treatment of ocular allergy, an ocular formulation of bilastine was developed. This is a preservative- and phosphate-free formulation containing sodium hyaluronate in a multidose bottle presentation for the treatment of allergic conjunctivitis. The most frequently used preservative, benzalkonium chloride, has demonstrated toxic effects in laboratory, experimental, and clinical studies, and can cause irritation, discomfort, and chronic inflammation [15,16]. Therefore, preservative-free eye drops are preferred whenever possible [11].

Here, we report the results of 2 clinical trials conducted to evaluate the efficacy of bilastine ophthalmic solution for treatment of the signs and symptoms of allergic conjunctivitis.

Methods

Study Design

Two clinical trials were conducted to assess the efficacy of bilastine ophthalmic solution for treatment of the signs and symptoms of allergic conjunctivitis. One was a single-site trial (phase 2 dose-ranging study, ClinicalTrials.gov number NCT03231969), and the other was a multicenter trial (phase 3 efficacy study, ClinicalTrials.gov number NCT03479307). Both studies used the Ora-Conjunctival Allergen Challenge (Ora-CAC®) model, which involves instillation of allergens directly into the eye to enable observation of acute allergic responses under controlled conditions [17].

Similar clinical protocols were employed for both trials, with the phase 2 dose-ranging study based on a 1:1:1:1 enrollment ratio (0.2% bilastine:0.4% bilastine:0.6% bilastine:vehicle) and a 6- to 10-week assessment period and the phase 3 efficacy study based on a 2:2:1 enrollment ratio (0.6% bilastine:0.025% ketotifen:vehicle) and a 5- to 9-week assessment period. The phase 2 dose-ranging study included 8 office visits, and the phase 3 efficacy study included 6 office visits (Table 1).

Both studies included a follow-up phone conversation 1 week after the last office visit. Institutional review of the protocol, protocol amendments, and informed consent complied with Good Clinical Practices, including the International Conference on Harmonisation Guidelines.

Patients

To be enrolled in either study, patients must have had a history of ocular allergies and a positive skin test reaction to a seasonal allergen (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, or cockroach). The inclusion criteria included written informed consent, age ≥18 years, willingness to discontinue wearing contact lenses for at least 72 hours prior to the start of the study and for the duration of the study, a negative urine pregnancy test (females of childbearing potential) and agreement to use an adequate method of birth control for the duration of the study, calculated visual acuity of 0.7 log of the minimum angle of resolution or better in each eye, a positive bilateral post-CAC reaction within 10 minutes of instillation of the allergen at visit 2, and a positive bilateral post-CAC reaction for at least 2 out of the first 3 time points following the challenge at visit 3.

Table 1. Study Schedule Outline.

Phase 2 dose-ranging study		Phase 3 efficacy study	
Visit	**Schedule**	**Visit**	**Schedule**
Visit 1 (day –50 to –22)	Screening/informed consent	Visit 1 (Day –50 to –22)	Screening/informed consent
Visit 2 (day –21±3)	Allergen titration	Visit 2 (day –21±3)	Allergen titration
Visit 3 (day –14±3)	Allergen confirmation	Visit 3 (day –14±3)	Allergen confirmation
Visit 4a (day 1)	Randomization/enrollment and instillation of first study treatment	Visit 4a (day 1)	Randomization/enrollment and instillation of first study treatment
Visit 4b (day 1, 16 h after visit 4a)	16-h duration of action	Visit 4b (day 1, 16 h after visit 4a)	16-h duration of action
Visit 5a (day 15±3)	Instillation second study treatment	Visit 5 (day 8±3)	15-min onset of action
Visit 5b (day 15 ±3, 8 h after visit 5a)	8-h duration of action	-	-
Visit 6 (Day 22 ±3)	15-min onset of action	-	-

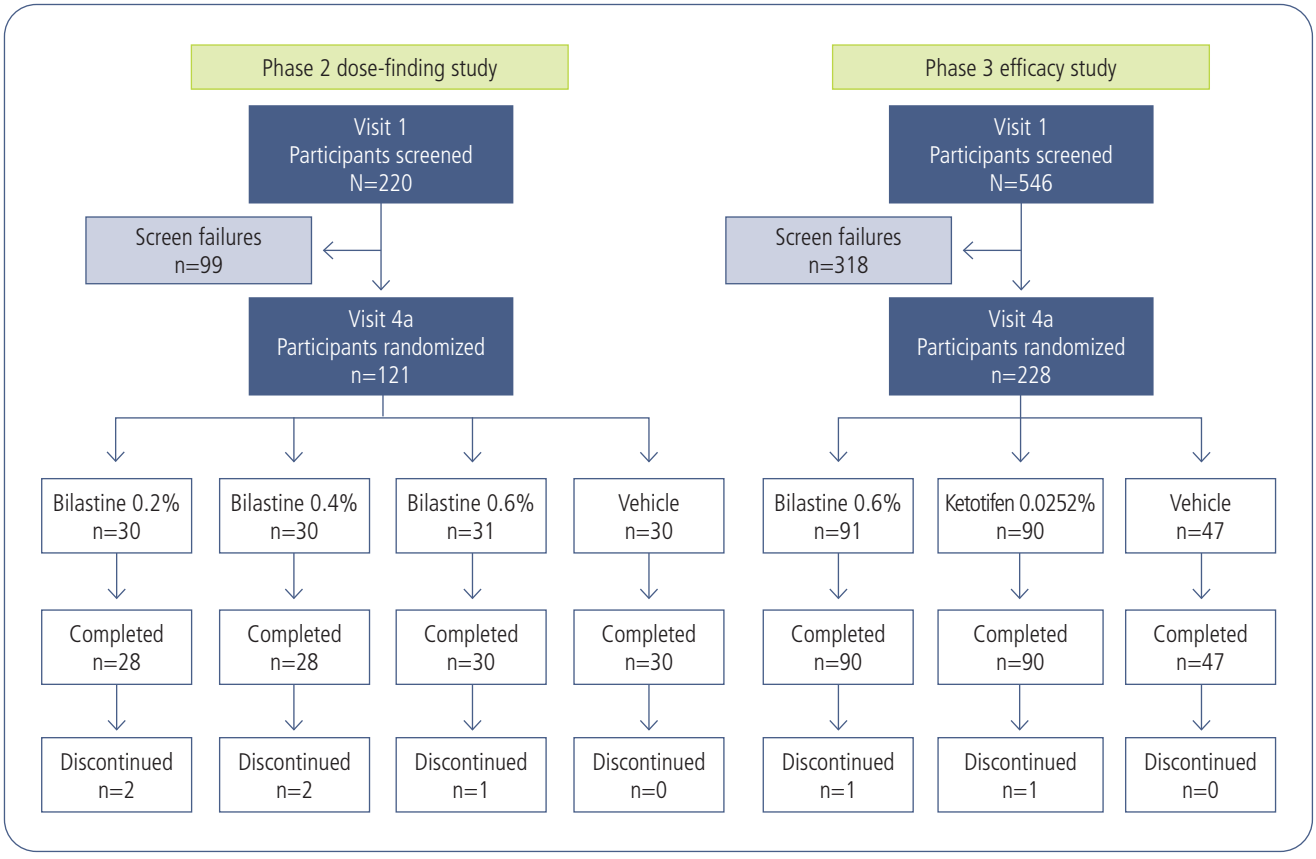

Figure 1. CONSORT flow chart.

Patients were excluded if they were sensitized to the investigational product, had an ocular condition that could have affected their safety or the trial parameters, had undergone an ocular surgical intervention within the previous 3 months or refractive surgery within the previous 6 months, or had been taking any disallowed medication including ophthalmological topical treatments (artificial tears, antihistamines, antihistamine/mast cell stabilizers, antihistamine-vasoconstrictor drug combinations, nonsteroidal anti-inflammatory drugs, or corticosteroids).

Study Objectives

The primary objectives of the phase 2 dose-ranging study were to assess the relative efficacy, safety, and duration of action of 3 concentrations of bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) compared with vehicle for treatment of the signs and symptoms of allergic conjunctivitis. The results of this study justified the optimal concentration and dosing regimen for phase 3 development. The primary objectives of the phase 3 efficacy study were to demonstrate the superiority of bilastine 0.6% ophthalmic solution over vehicle for the treatment of patient-assessed ocular itching (assessed 3, 5, and 7 minutes post-CAC) at the onset of action and after 16 hours of action, and to demonstrate the noninferiority of multidose preservative-free bilastine 0.6% to multidose ketotifen 0.025% with preservatives at the onset of action visit. As ketotifen 0.025% is indicated for twice-daily dosing, comparisons to bilastine at 16 hours were not made.

Table 2. Demographic Profile and Baseline Characteristics.

	Phase 2 dose-ranging study				
	Bilastine 0.2% (n=30)	**Bilastine 0.4% (n=30)**	**Bilastine 0.6% (n=31)**	**Vehicle (n=30)**	**All patients (N=121)**
Mean (SD) age, y	50.4 (10.7)	47.0 (14.0)	51.8 (13.1)	48.3 (13.2)	49.4 (12.8)
Female sex, No. (%)	16 (53.3)	18 (60.0)	15 (48.4)	17 (56.7)	66 (54.5)
Race, No. (%)					
American Indian or Alaskan Native	0	1 (3.3%)	0	0	1 (0.8)
Asian	1 (3.3)	0	1 (3.2)	0	2 (1.7)
Black or African American	1 (3.3)	2 (6.7)	4 (12.9)	3 (10.0)	10 (8.3)
White	27 (90.0)	27 (90.0)	26 (83.9)	27 (90.0)	107 (88.4)
Multiple	1 (3.3)	0	0	0	1 (0.8)
Mean (SD) baseline ocular itching (visit 3, day –14)					
Pre-CAC	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	–
3 min post-CAC	2.75 (0.57)	2.98 (0.57)	2.69 (0.75)	2.92 (0.61)	–
5 min post-CAC	3.14 (0.53)	3.32 (0.46)	2.99 (0.60)	3.31 (0.56)	–
7 min post-CAC	3.21 (0.50)	3.39 (0.54)	3.07 (0.58)	3.33 (0.57)	–
	Phase 3 efficacy study				
	Bilastine 0.6% (n=91)	**Ketotifen 0.025% (n=90)**	**Vehicle (n=47)**	**All patients (N=228)**	
Mean (SD) age, y	45.9 (12.88)	41.7 (12.10)	45.1 (16.03)	44.1 (13.38)	
Male sex, No. (%)	58 (63.7)	53 (58.9)	25 (53.2)	136 (59.6)	
Race, No. (%)					
American Indian or Alaskan Native	1 (1.1)	1 (1.1)	1 (2.1)	3 (1.3)	
Asian	14 (15.4)	13 (14.4)	6 (12.8)	33 (14.5)	
Black or African American	25 (27.5)	27 (30.0)	14 (29.8)	66 (28.9)	
White	49 (53.8)	48 (53.3)	26 (55.3)	123 (53.9)	
Multiple	2 (2.2)	1 (1.1)	0	3 (1.3)	
Mean (SD) baseline ocular itching (visit 3, day –14)					
Pre-CAC	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	–	
3 min post-CAC	2.71 (0.61)	2.71 (0.70)	2.61 (0.6)	–	
5 min post-CAC	2.98 (0.58)	2.99 (0.56)	2.91 (0.47)	–	
7 min post-CAC	3.09 (0.59)	3.04 (0.54)	2.97 (0.51)	–	

Abbreviation: CAC, Ora-Conjunctival Allergen Challenge.

A secondary objective of the phase 3 efficacy study was to demonstrate the superiority of bilastine over vehicle for the treatment of conjunctival redness.

Efficacy Variables

The primary efficacy measure for the phase 2 dose-ranging study was ocular itching evaluated by the patient after CAC at the onset of action (15 minutes after instillation) and 8 hours and 16 hours after instillation using the Ora Calibra ocular itching scale (scored 0 to 4, where 0=none and 4=very severe). The primary efficacy measure for the phase 3 efficacy study was ocular itching evaluated by the patient after CAC at the onset of action (15 minutes after instillation) and after 16 hours of action using the same 0-4 scale. Ocular itching at onset of action was then compared with ketotifen to evaluate noninferiority of bilastine 0.6% to ketotifen 0.025%. Secondary efficacy measures included conjunctival redness evaluated by the investigator using the Ora Calibra ocular redness scale (scored 0 to 4, where 0=none and 4= extremely severe), measured in both the phase 2 dose-ranging study and the phase 3 efficacy study.

Statistical Analysis

All randomized patients who received the study medication were included in the intent-to-treat population as used for all analyses. The primary efficacy analyses were conducted using analysis of covariance (ANCOVA) models with last observation carried forward for missing data. These models included treatment and the average of the patients' post-CAC scores at visit 3 as covariates. Least square (LS) means were estimated for each treatment and for the difference between each active treatment and vehicle at each visit and time point. In addition, ANCOVA models were run at 15 minutes, 8 hours (for the phase 2 dose-ranging study), and 16 hours after instillation, with treatment, time point, and time-appropriate baseline as covariates for adjustment (accounting for repeated measurements). LS means for each treatment and for the difference between each active treatment and vehicle (along with the corresponding 95%CI) were calculated at each visit and time point from these repeated-measures ANCOVA models. Two-sample *t* tests were used as unadjusted sensitivity analyses at each post-CAC time point.

The number of patients with ocular itching scores reduced by 50% were summarized with counts and percentages by treatment group for each post-CAC time point at 15 minutes, 8 hours (for the phase 2 dose-ranging study only), and 16 hours after instillation. The proportion of responders at each visit was compared between treatment groups using the Fisher exact test.

To demonstrate the noninferiority of bilastine 0.6% to ketotifen 0.025% for the treatment of ocular itching, bilastine 0.6% had to demonstrate statistical noninferiority to ketotifen 0.025% within 0.4 units for all 3 post-CAC time points, ie, 3, 5, and 7 minutes, at 15 minutes after instillation (for the phase 3 efficacy study). Conjunctival redness was analyzed using the same populations and missing data methods as for the primary endpoint.

Results

Study Population

A total of 349 patients were randomized (bilastine 0.2%, n=30; bilastine 0.4%, n=30; bilastine 0.6%, n=122; ketotifen 0.025%, n=90; and vehicle, n=77), and 343 patients completed the 2 studies and were included in the data analysis. The progress of patients through the trial is shown in a CONSORT flow diagram (Figure 1).

The demographic profile and baseline characteristics were similar across both studies and treatment groups (Table 2).

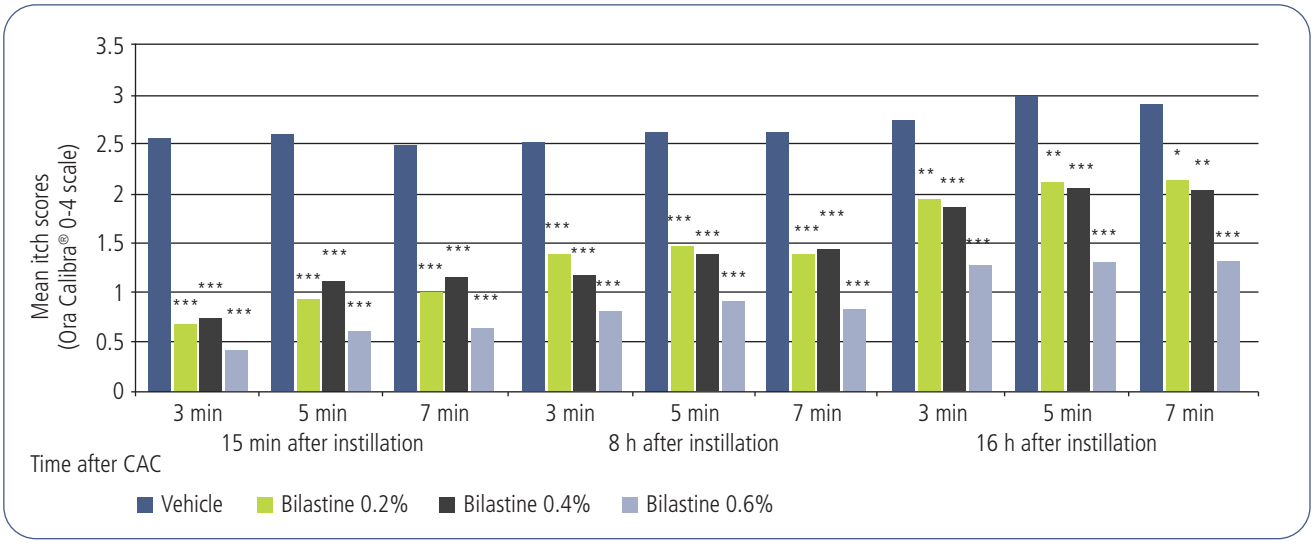

Figure 2. Mean itch scores across concentrations of bilastine in the phase 2 dose-ranging study. Bars represent the ANCOVA LS mean itch score for vehicle and each concentration of bilastine (0.2%, 0.4%, and 0.6%) for each time point after CAC (3, 5, and 7 minutes) and for each study visit, where 15 minutes after installation is visit 6, 8 hours after instillation is visit 5b, and 16 hours after instillation is visit 4b. Significance compared to the mean itch score of the vehicle (*, $P<.05$; **, $P<.001$; ***, $P<.0001$, 2-sample *t* test). CAC indicates conjunctival allergen challenge; ANCOVA, analysis of covariance; LS, least squares.

Efficacy Analysis

Phase 2 Dose-Ranging Study

The primary efficacy measure of ocular itching induced by the CAC was assessed by patients in each eye using the Ora Calibra ocular itching scale at 15 minutes, 8 hours, and 16 hours after instillation. All 3 bilastine concentrations significantly reduced ocular itching compared to vehicle for all 3 post-CAC time points, for both onset of action and duration of action (Figure 2). Bilastine 0.6% demonstrated the greatest statistically significant differences between treatment and vehicle (with *P*<.0001 at all 3 post-CAC time points for all 3 postinstillation time points).

In addition to the statistical assessments of itch responses, clinical significance was also examined using the 50% responder rate as a metric of efficacy. This rate establishes a cut-off, ie, a 50% reduction in individual patient itch scores, as an indication of a clinically significant reduction. As shown in Figure 3A, significant clinical relief of ocular itching was observed at 15 minutes and 8 hours after instillation compared to placebo for all doses of bilastine (15 minutes: 71.4% of patients with >50% reduction in ocular itching for bilastine 0.2%, 75.0% for bilastine 0.4%, and 83.3% for bilastine 0.6%; 8 hours: 44.8% for bilastine 0.2%, 35.7% for bilastine 0.4%, and 76.7 for bilastine 0.6%; 16 hours: 10.0% for bilastine

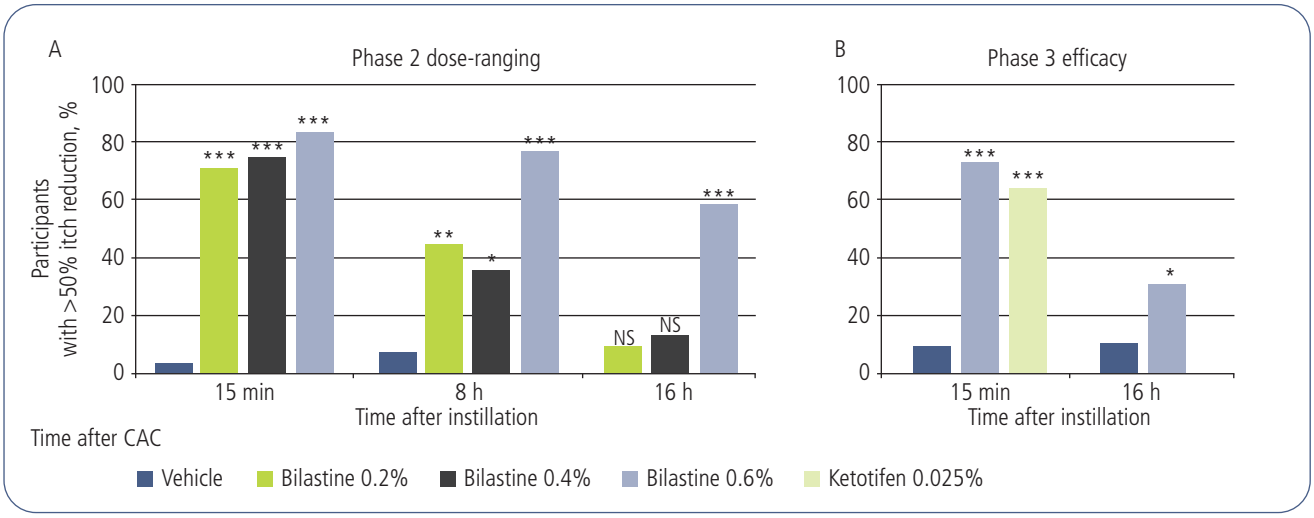

Figure 3. Responder analysis. Percentage of patients with > 50% itch reduction in the phase 2 dose-ranging study and the phase 3 efficacy study. Bars represent the percentage of patients with a >50% reduction in mean itch score (as measured on the 0-4 scale) at A) 15 minutes after instillation (visit 6), 8 hours after instillation (visit 5b), 16 hours after instillation (visit 4b) and B) 15 minutes after instillation (visit 5) and 16 hours after instillation (visit 4b). Significance compared to placebo in the percentage of patients with a >50% reduction in the itch score (NS, not significant; *, *P*<.05; **, *P*<.001; ***, *P*<.0001, Fisher exact test). CAC indicates conjunctival allergen challenge.

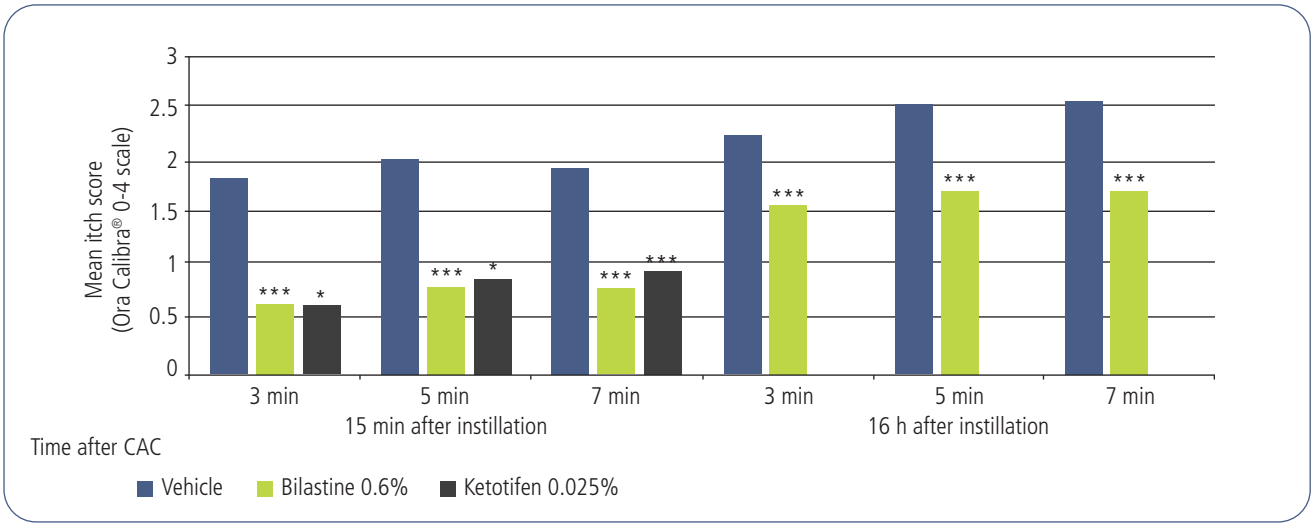

Figure 4. ANCOVA LS mean itch responses to bilastine or ketotifen, phase 3 efficacy study. Bars represent the ANCOVA LS mean itch score for vehicle, bilastine 0.6%, and ketotifen 0.025% for each time point after CAC (3, 5, and 7 minutes) and for each study visit, where 15 minutes after installation is visit 5 and 16 hours after instillation is visit 4b. Significance compared to the mean itch score of the vehicle (*, *P*<.05; **, P<.001; ***, *P*<.0001, 2-sample *t* test). CAC indicates conjunctival allergen challenge; ANCOVA, analysis of covariance; LS, least squares.

0.2%, 13.3% for bilastine 0.4%, and 58.1% for bilastine 0.6%). Compared to placebo, bilastine 0.6% also provided clinically significant relief at 16 hours after instillation (58.1% of patients with >50%). Based on these results, bilastine 0.6% was found to be the optimal dose and was selected for use in the phase 3 efficacy study.

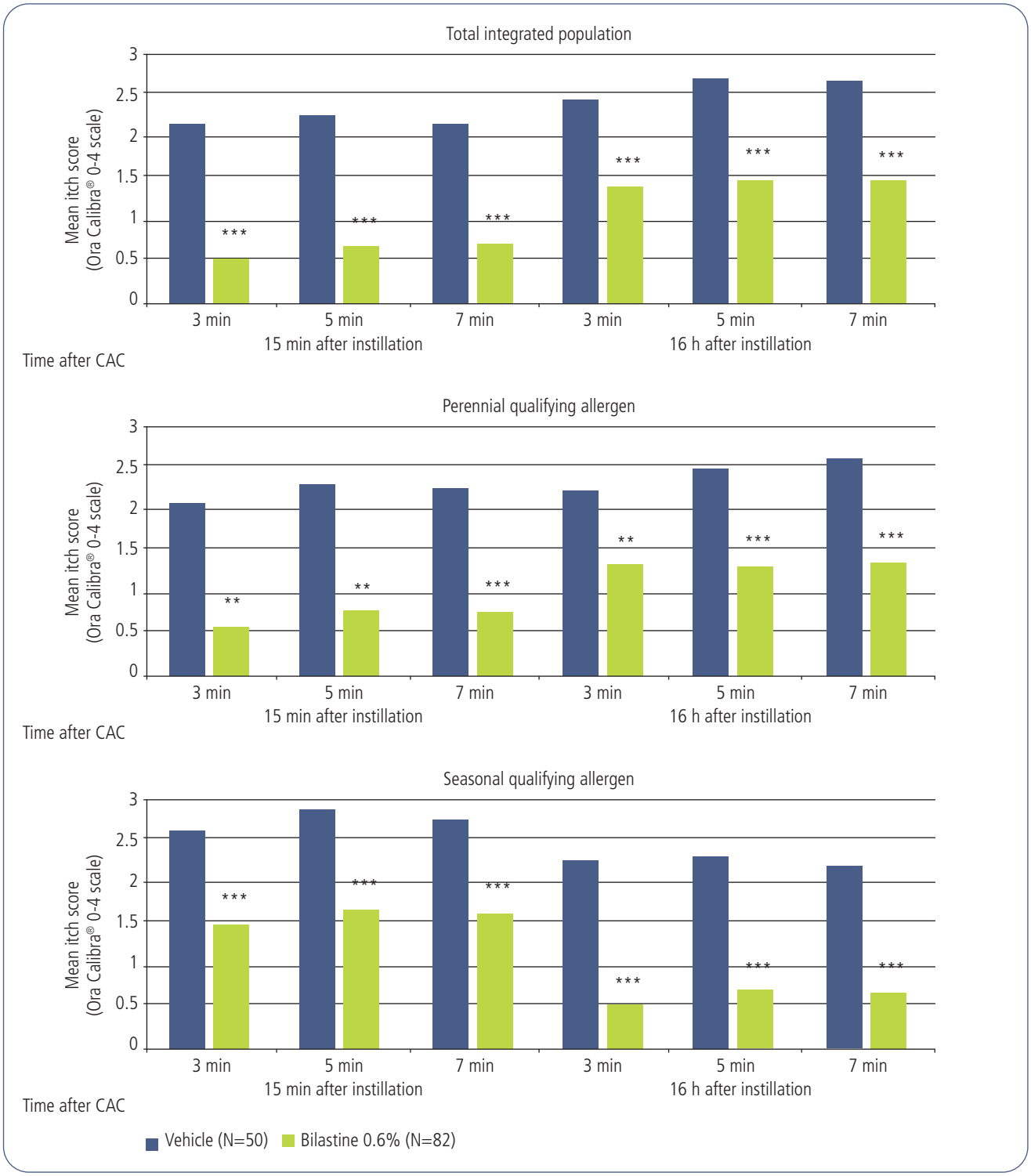

Figure 5. ANCOVA LS mean itch analysis for the integrated data set. Bars represent the ANCOVA LS mean itch score for vehicle and bilastine 0.6% for each time point after CAC (3, 5, and 7 minutes) and for each study visit, where 15 minutes after installation is visit 5 and 16 hours after instillation is visit 4b. Significance (*, $P<.05$; **, $P<.001$; ***, $P<.0001$, 2-sample *t* test) compared to the mean itch score of the vehicle. CAC indicates conjunctival allergen challenge; ANCOVA, analysis of covariance; LS, least squares.

For the key secondary efficacy endpoint of conjunctival redness, treatment differences resulted in *P* values of <.05 for bilastine 0.6% compared to vehicle at 7 minutes after CAC and at 15 minutes, 8 hours, and 16 hours after instillation and for bilastine 0.4% at 7 minutes after CAC and at 15 minutes after instillation (data not shown). Bilastine ophthalmic solution appears to be safe and well tolerated. Similar numbers of treatment emergent adverse events (TEAEs) were reported in the bilastine 0.2% group (8 TEAEs) and in the vehicle group (7 TEAEs), with fewer TEAEs reported in the bilastine 0.4% group (3 TEAEs) and the bilastine 0.6% group (1 TEAE).

Phase 3 Efficacy Study

The primary efficacy measure of ocular itching was assessed for each eye by patients after CAC 15 minutes and 16 hours after instillation. All itch measures were significantly lower for bilastine 0.6% than for vehicle (*P*<.0001 for 3, 5, and 7 minutes after CAC) for 15 minutes and 16 hours after instillation (Figure 4). These improvements were ≥1 unit compared to vehicle at all 3 time points 15 minutes after instillation, with the greatest mean treatment difference occurring at 5 minutes after CAC (unadjusted mean treatment difference, –1.183; LS mean treatment difference, –1.208).

To demonstrate the noninferiority of bilastine 0.6% to ketotifen 0.025% for the treatment of ocular itching, bilastine 0.6% had to demonstrate statistical noninferiority to ketotifen 0.025% within 0.4 units for all 3 post-CAC time points, namely, 3, 5, and 7 minutes at 15 minutes after instillation (visit 5). Comparison of the bilastine 0.6% and ketotifen 0.025% groups demonstrated that bilastine 0.6% was noninferior at all 3 post-CAC time points for onset of action (15 minutes after instillation), based on an inferiority margin of 0.4 (mean treatment difference of 0.009, –0.077, and –0.159 for 3, 5, and 7 minutes, respectively, after CAC for 15 minutes after instillation).

As in the phase 2 study, the clinical significance of reduced itching was also examined using the >50% responder rate as a metric of efficacy. As shown in Figure 3B, significant clinical relief of ocular itching was observed at 15 minutes for bilastine 0.6% (72.2% of patients had a >50% reduction in itch), demonstrating the quick onset of action of the formulation. For the key secondary efficacy endpoint of conjunctival redness, treatment differences resulted in *P* values of <.05 for bilastine 0.6% compared to vehicle at 7, 15, and 20 minutes after CAC at 15 minutes after instillation. A total of 6 patients (2.6%) experienced TEAEs; all of these were mild in severity, and none were considered treatment-related.

Integrated Data Set

As a supplement to the individual results of the 2 studies, data from the phase 2 dose-ranging study were combined with data from the phase 3 efficacy study to create a larger, integrated data set. The integrated population mean itch scores exhibited the same efficacy as those from the individual studies: differences between vehicle and bilastine 0.6% were significant at all time points both at onset (15 minutes) and at a prolonged duration (16 hours) after instillation (Figure 5). The 2 subpopulations examined, ie, perennial and seasonal qualifying allergen, also displayed consistently high efficacy across all measures of ocular itching (Figure 5). This confirms that the overall results were not associated with a strong preferential effect of the drug on itching due to a specific type of allergen.

As a final assessment of the integrated data set, a responder analysis was conducted to determine the clinical significance of relief from itching observed in the pooled data sets (Figure 6). While the 2 subpopulations derived from the pooled analysis differed in size (there are about twice as many patients with seasonal allergens as those with perennial allergens), they are similar in all other characteristics. This was also observed in

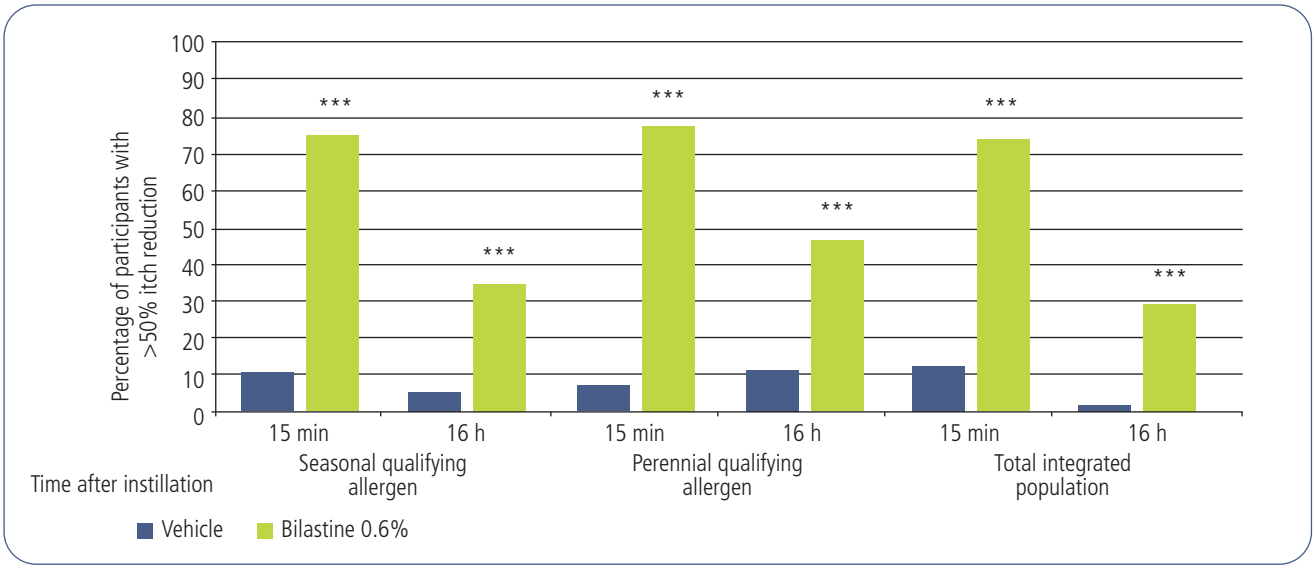

Figure 6. Responder analysis. Percentage of patients with >50% reduction in itch at all time points, integrated data set. Bars represent the percentage of patients with a >50% reduction in mean itch score (as measured on the 0-4 scale) at 15 minutes after instillation and 16 hours after instillation. Significance (*, *P*<.05; **, *P*<.001; ***, *P*<.0001, Fisher exact test) indicates difference compared to placebo in the percentage of patients with a >50% reduction in itch score.

the responder analysis, where a clinical response was seen in the same proportion of patients in all groups at the onset of action and after 16 hours.

Discussion

Bilastine has previously been shown to be effective in the treatment of rhinitis and allergic conjunctivitis as an oral formulation [14,18]. The present work demonstrates the efficacy of bilastine as an ophthalmic solution for treatment of allergic conjunctivitis. In a phase 2 clinical trial, efficacy was achieved for the primary efficacy endpoint of ocular itching for 3 bilastine concentrations (0.2%, 0.4%, and 0.6%) at 15 minutes and 8 hours after instillation [19]. In a subsequent phase 3 study, bilastine 0.6% ophthalmic solution was efficacious at 15 minutes and 16 hours after instillation, demonstrating its usefulness in terms of onset and duration of action. Moreover, bilastine 0.6% demonstrated noninferiority to ketotifen 0.025% ophthalmic solution at 15 minutes after installation [20].

The integrated data set strongly supported the findings of the individual studies, showing that patients who received bilastine 0.6% ophthalmic solution had a significantly lower mean itch score at all post-CAC time points at both 15 minutes after instillation (onset of action) and 16 hours after instillation (duration of action). Furthermore, a significantly larger percentage of patients in the active group had a >50% reduction in individual itch scores than in the placebo group, demonstrating a significant improvement in itching associated with allergic conjunctivitis.

Bilastine 0.6% solution is the first direct formulated multidose preservative-free ophthalmic solution with sodium hyaluronate formulated for once-daily administration in the treatment of allergic conjunctivitis. Moreover, to improve adherence, the goal is to maximize convenience for the patient by reducing the number of instillations per day and minimizing the potential irritant and toxic effects of preservative compounds on the ocular surface. Furthermore, ophthalmic solutions containing preservatives such as benzalkonium chloride cannot be used concurrently with contact lenses [11,21]. Since there is no preservative in bilastine ophthalmic solution, previous preclinical studies have demonstrated that the formulation does not interfere with soft contact lenses (data not shown).

A possible limitation that must be considered when interpreting our results is that in the phase 3 study, the ketotifen administered contained a preservative, because there were no commercially available multidose ophthalmic formulations of preservative-free ketotifen when the study was planned and conducted. The ketotifen multidose formulation with preservatives was selected to homogenize the administration device in multidose containers and maintain a double-blind study.

In both studies, bilastine ophthalmic solution demonstrated a favorable safety and efficacy profile for the treatment of ocular itching and better patient-reported comfort scores in experimental conjunctival challenge tests. Further studies are necessary to demonstrate similar outcomes in daily clinical practice. Overall, the results of these 2 studies are strongly supportive of bilastine 0.6% ophthalmic solution for the treatment of ocular itching associated with allergic conjunctivitis while protecting ocular surface homeostasis.

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Conflicts of Interest

PJG is an employee of Ora, Inc. JBC is a consultant to Ora, Inc. PA, AG, GH, and NF are employees of FAES Farma.

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