ORIGINAL ARTICLE

Efficacy of Once-Daily Ophthalmic Bilastine for the Treatment of Allergic Conjunctivitis: A Dose-Finding Study

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Abstract

Background and objectives: Bilastine is a nonsedating second-generation antihistamine for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. Our study aimed to evaluate the optimal dose, efficacy, and safety of a newly developed once-daily preservative-free ophthalmic formulation of bilastine for allergic conjunctivitis.
Methods: Our phase 2, single-center, double-masked, randomized trial compared the efficacy of 3 doses of a bilastine ophthalmic formulation (0.2%, 0.4%, and 0.6%) with that of vehicle for the treatment of allergic conjunctivitis. The primary efficacy endpoint was the reduction in ocular itching. The Ora-CAC Conjunctival Allergen Challenge model was used to assess ocular and nasal symptoms at the onset of action (15 minutes) and at 8- and 16-hours after treatment. Tolerance and safety were also evaluated.
Results: A total of 121 adults with seasonal and/or perennial ocular allergy were randomized. Bilastine ophthalmic formulations 0.2%, 0.4%, and 0.6% were significantly superior ($P>.001$) to vehicle for the treatment of ocular itching at 3, 5, and 7 minutes after challenge at onset of action (15 minutes) and at 8 hours after treatment. Bilastine 0.6% was also effective at 16 hours after treatment. Treatment differences for bilastine 0.6% were statistically significant ($P<.001$) compared to vehicle at all timepoints for tearing, eyelid swelling, and nasal symptoms. No relevant adverse events were observed.
Conclusions: All the tested ophthalmic bilastine doses were efficacious for rapid reduction of ocular itching. The 0.6% formulation was effective up to 16 hours after treatment, making it suitable for once-daily administration. The new formulation was safe and well tolerated.

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

Resumen

Introducción y objetivos: Bilastina es un antihistamínico no sedante de segunda generación para el tratamiento sintomático de la rinoconjuntivitis alérgica y la urticaria. El objetivo de este ensayo clínico fue evaluar la dosis óptima, la eficacia y la seguridad de una formulación oftálmica de bilastina, sin conservantes y de administración única diaria, recientemente desarrollada para el tratamiento de la conjuntivitis alérgica.
Métodos: Este estudio aleatorizado doble ciego de fase 2, realizado en un solo centro, evaluó la eficacia de 3 dosis de la formulación oftálmica de bilastina (0,2%, 0,4% y 0,6%) comparado con placebo para el tratamiento de la conjuntivitis alérgica. La variable principal de eficacia fue la reducción del prurito ocular. Se utilizó el modelo de provocación conjuntival, Ora-CAC® *Conjunctival Allergen Challenge*, para evaluar los síntomas oculares y nasales a los 15 minutos (inicio de acción) tras la administración del fármaco, y 8 horas y 16 horas después del tratamiento. También se evaluaron la tolerancia y la seguridad.
Resultados: Se aleatorizaron un total de 121 adultos con alergia ocular estacional y/o perenne. Las formulaciones oftálmicas de bilastina 0,2%, 0,4% y 0,6% fueron significativamente superiores ($p>0,001$) a placebo en el tratamiento del prurito ocular evaluado a los 3, 5 y 7 minutos tras la provocación (15 minutos) y 8 horas después del tratamiento. Además, bilastina 0,6% también fue eficaz 16 horas después de su aplicación inicial. Las diferencias entre tratamientos fueron estadísticamente significativas ($p<0,001$) para bilastina 0,6% en comparación con el placebo para lagrimeo, edema de los párpados y síntomas nasales en todos los tiempos analizados. No se observaron acontecimientos adversos relevantes.
Conclusiones: Todas las dosis de bilastina oftálmica evaluadas fueron eficaces para reducir rápidamente el prurito ocular. La formulación de 0,6% fue eficaz hasta 16 horas después de la aplicación, lo que la hace adecuada para su administración una vez al día. La nueva formulación fue segura y bien tolerada.

Palabras clave: Conjuntivitis alérgica. Antihistamínico. Prurito ocular. Bilastina. Una vez al día. Sin conservantes.

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. However, an ophthalmic formulation would be preferred for patients with allergic conjunctivitis to ensure faster onset of action, improved effectiveness, and better tolerability.

- **How does this study impact our current understanding and/or clinical management of this topic?**

  This study shows that a newly developed once-daily, preservative-free, ophthalmic formulation of bilastine is efficacious for rapid reduction of ocular itching in patients with allergic conjunctivitis. Ophthalmic bilastine 0.6% was effective for 16 hours and was safe and well tolerated.

Introduction

Allergic conjunctivitis (AC) is a highly prevalent hypersensitivity disorder of the conjunctiva affecting up to 40% of the adult population [1]. It is frequently concomitant with allergic rhinitis, although some patients (6%-30%) can develop ocular symptoms without nasal involvement [2,3]. The symptoms of AC include ocular itching, conjunctival redness, and tearing and may have a significant impact on quality of life [4,5]. Current treatments aim to control and relieve symptoms and include systemic or topical antihistamines, mast cell stabilizers, dual-action agents, anti-inflammatory drugs, and corticosteroids [6,7]. Topical ocular antihistamines are a common treatment in cases of isolated ocular symptoms.

Bilastine is a second-generation antihistamine approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria [8-10]. Based on clinical evidence in adults and adolescents older than 12, oral 20 mg was approved in Europe in 2010. Further evidence in younger children from the Pediatric Investigation Plan (PIP) led to approval for bilastine (10 mg) in Europe in a stepwise procedure. The drug is currently approved in children aged 6-11 years who weigh ≥20 kg. However, other regulatory agencies have approved the drug for children older than 2 years [10,11].

The preclinical pharmacology study of bilastine revealed that toxicity occurred only at levels significantly higher than the proposed topical ocular dose [12,13]. Oral bilastine has proven to significantly reduce the ocular symptoms of allergic rhinoconjunctivitis [14-17], and its safety has been extensively characterized. Twenty phase 1 studies performed in healthy volunteers [18,19], and 10 phase 2 and 3 studies conducted in patients, one with a 1 year long-term extension phase, show that bilastine 20 mg has an excellent safety and tolerability profile, with most adverse events described as either mild or moderate and none found to be more frequent than in the placebo group [14,20,21,17,22,16]. The safety profile of bilastine in children, adolescents, and elderly patients has been shown to be similar to that in adults [23-27]. Likewise, postauthorization noninterventional studies of bilastine have analyzed over 13 300 patients, and no new safety findings have arisen that would alter the known safety profile of the molecule. Moreover, oral bilastine has been shown to improve the quality of life of patients with AC [28] and meets the current Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines for medications used in the treatment of allergic rhinitis [29].

If ocular symptoms prevail, topical antihistamines are usually preferred to oral antihistamines because of their faster onset of action and effectiveness, together with their lower incidence of adverse effects [10]. However, adherence decreases if several daily instillations are required, as shown by studies on adherence in other ocular conditions [30]. To minimize the possible toxic effects of preservative compounds on the ocular surface and ensure compliance, single dose preservative-free eye drops should be used whenever possible [6]. Therefore, a once-daily, preservative-free, ophthalmic formulation of bilastine has been developed for the specific treatment of allergic conjunctivitis. Preclinical in vivo biodistribution and pharmacokinetic studies of this formulation in humans showed that bilastine is predominantly distributed in the conjunctiva, the intended target tissue, while it is poorly absorbed in the bloodstream [31,32].

To assess the efficacy and safety of ophthalmic bilastine, we designed a study whose methodology was based on the Ora-CAC Conjunctival Allergen Challenge (CAC) model, which allows for a high degree of reproducibility and internal control [33,34]. The CAC model has been extensively used to evaluate the inflammatory effects of an allergen after topical application on the external ocular surface and to evaluate the effect of various antihistamines [35]. This methodology is recommended by the European Academy of Allergy and Clinical Immunology [36] and is a standardized testing model for registration purposes by the United States Food and Drug Administration, the European Medicines Agency, and the Japanese Pharmaceuticals and Medical Devices Agency. Here We describe the results of our dose-finding, vehicle-controlled, randomized clinical trial, which evaluated the efficacy, safety, and tolerance of 3 doses of bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) for the symptomatic treatment of AC.

Methods

This phase 2, single-center, randomized, double-masked, vehicle-controlled, CAC trial was carried out at the Ora Clinical Research Center in Andover, Massachusetts, USA between September 8, 2017 (first patient enrolled) and October 11, 2017 (last patient completed treatment).

The study compared the efficacy of 3 doses of bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) with that of vehicle (formulation without bilastine) for the treatment of AC,

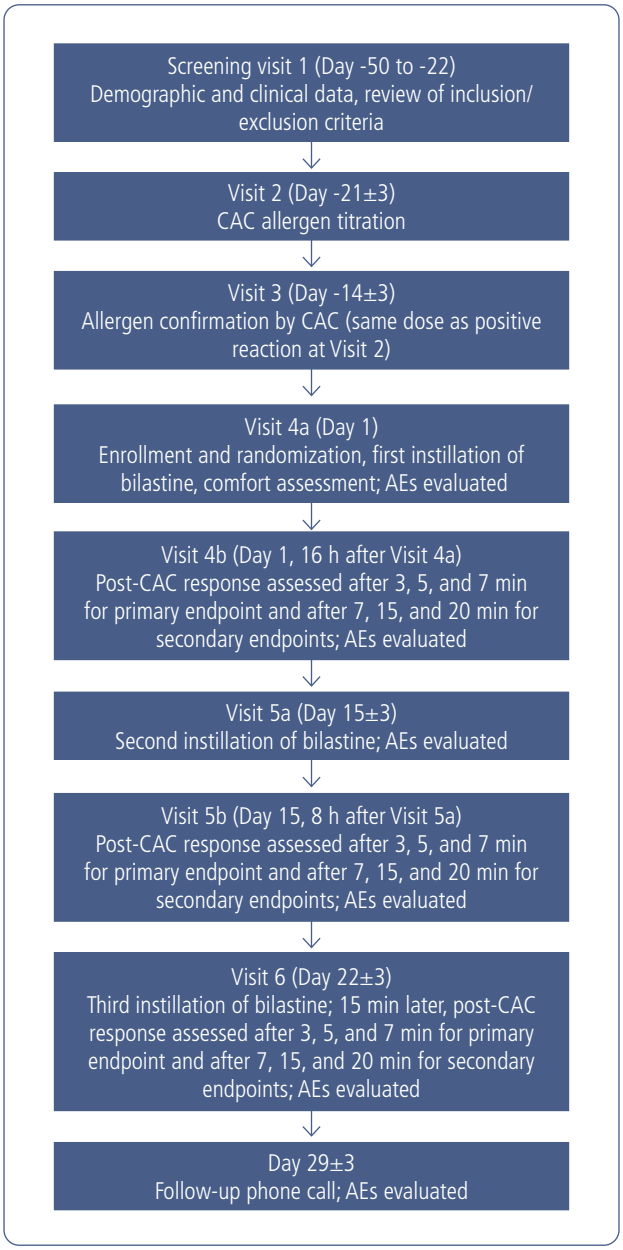

Figure 1. Study design according to the conjunctival allergen challenge model. AEs indicates adverse events; CAC, conjunctival allergen challenge.

as well as safety and tolerability. Efficacy was evaluated using the Ora-CAC model (Ora Inc) [33], in which the allergen is titrated directly into the eye under controlled conditions until a positive clinical response is observed. Once reproducibility of the allergic reaction is confirmed, the efficacy of the study drug is tested in combination with the CAC model to evaluate and measure the signs and symptoms of AC. The timepoints for evaluating efficacy in ocular itching and conjunctival redness were based on previous studies with the CAC model [33,34,37,38].

The study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines [39], and all patients gave their informed consent. The study protocol, informed consent form, assent form, Health Information Portability and Accountability form, print advertisement, screening and enrollment form, and primary care physician notification form were reviewed by a properly constituted Alpha institutional review board. The study was registered with ClinicalTrials.gov (identifier NCT03231969).

Study Design

Figure 1 shows the study design. After a screening visit to review inclusion and exclusion criteria (see below), patients underwent a bilateral CAC to titrate an allergen and evaluate individual allergic sensitivity (visit 2). One drop per eye of a solubilized allergen to which the patient was sensitized was administered at the weakest dilution into the conjunctival sac.

If the patient failed to react within 10 (±2) minutes, increasing concentrations were instilled at approximately 10-minute intervals until a positive bilateral reaction was elicited. If a positive CAC reaction was not elicited with the first allergen, other allergens to which the patient was sensitized were used, starting at the lowest dose. At all subsequent visits, patients received the same type of allergen and concentration identified at visit 2. Upon completion of the initial CAC titration, patients underwent an ocular examination by the investigator to evaluate all efficacy measures and confirm the patient's eligibility. Patients were also asked to self-assess their ocular and nasal allergic symptoms using the Ora-CAC scales. Any patient whose result was not positive was excluded from the study.

At visit 3, patients were evaluated for visual acuity using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and underwent slit lamp biomicroscopy. Ocular and nasal allergic signs and symptoms were assessed before CAC by the investigator and patient using the Ora Calibra clinical grading scales. These evaluations were carried out at all subsequent visits. At visit 3, a confirmation CAC was also conducted.

Duration of action after 16 hours of drug instillation was assessed at visit 4, which was divided into 2 phases, visits 4a and 4b. At visit 4a, patients who qualified to continue in the study were randomized to 1 of the 4 treatment groups: 0.2%, 0.4%, 0.6% bilastine ophthalmic formulation (FAES Farma), or vehicle. Then, a trained study technician instilled the assigned study drug solution 16 (±1) hours before the CAC was performed. After drug instillation (visit 4a), patients rated comfort in each eye using the Ora Calibra Drop Comfort Scale and described how the study drug instillation felt using the Ora Calibra Drop Comfort Questionnaire.

At visit 4b, which was 16 (±1) hours after study drug instillation (visit 4a), each patient received bilaterally 1 drop of the allergen solution of the type and dose that elicited a positive reaction at visit 2. Ocular and nasal allergic signs and symptoms were assessed after CAC by the investigator and the patient at the predetermined timepoints using the Ora Calibra grading scales. Once patients received the first study drug, adverse events were considered to be treatment-emergent adverse events (TEAEs) and assessed after CAC from visit 4b onwards.

Visits 5a and 5b followed same protocol as visits 4a and 4b, although the interval between the administration of the study drug at visit 5a (bilastine ophthalmic solutions or vehicle) and the CAC at visit 5b was 8 (±1) hours.

At visit 6, the study drug (bilastine solutions or vehicle) was applied 15 (±1) minutes before CAC. Intraocular pressure was measured in each eye using contact tonometry. A dilated fundoscopy exam was performed by the investigator. A follow-up phone call was conducted about 1 week after visit 6 to evaluate any TEAEs.

Study Population

The inclusion criteria for participants were as follows: asymptomatic patients aged ≥18 years with a history of AC 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, cockroach); a positive bilateral post-CAC reaction (defined as having scores of ≥2 for ocular itching and conjunctival redness) within 10±2 minutes of instillation of the last titration of allergen at visit 2; a positive bilateral post-CAC reaction for at least 2 out of the first 3 timepoints following the challenge at visit 3; calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart; and providing informed consent.

The exclusion criteria were as follows: contraindications or sensitivities to bilastine or the vehicle; having any ocular condition that, in the investigators' opinion, could affect the patient's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium, or dry eye); having a known history of retinal detachment, diabetic retinopathy, or active retinal disease; using any of the disallowed medications during the period indicated prior to visit 2 and during the study (systemic antihistamines, decongestants, monoamine oxidase inhibitors, all topical ophthalmic preparations, lid scrubs, prostaglandins, nonsteroidal anti-inflammatory drugs, corticosteroids, depo-corticosteroids); manifesting signs or symptoms of clinically active AC in either eye at the start of visits 2, 3, or 4a (defined as the presence of any itching or >1 for redness in any vessel bed); significant illness the investigator felt could be expected to interfere with the patient's health or with the study parameters; or pregnancy.

Efficacy Endpoints and Assessments

The primary efficacy endpoint was ocular itching evaluated by the patient at the following timepoints: 3 (±1), 5 (±1), and 7 (±1) minutes after CAC; at visits 4b (16 hours after study drug administration), 5b (8 hours after study drug administration), and 6 (15 minutes after study drug administration), based on the Ora Calibra scale, which was graded as 0=none and 4=very severe (0.5 unit increments allowed) [40]. Significant efficacy for ocular itching (primary endpoint) for all bilastine ophthalmic solutions over vehicle was established at 0.5 units on a 5-point scale for all 3 post-CAC timepoints (3 [±1], 5 [±1], and 7 [±1] minutes after CAC) at 1 of 3 study visits, and at least 1 unit for most (2:3) of these post-CAC timepoints, although clinically significant relevance has been considered to be at least 1 unit over 5.

The secondary efficacy endpoints were measured 7, 15, and 20 minutes after CAC at visits 4b, 5b, and 6 on a scale of 0 to 4, where 0=none, except for eyelid swelling, which used a 0 to 3 scale, with 0=none. Secondary outcomes, conjunctival redness (main), ciliary redness, episcleral redness, and chemosis were evaluated by the investigator; eyelid swelling, tearing, rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion were evaluated by the patient.

An exploratory efficacy endpoint was also assessed as ocular itching and redness summarized by allergen type (seasonal and perennial).

Safety and Tolerability Endpoints

The safety endpoints were as follows: adverse events at all office visits; visual acuity using the ETDRS chart at visits 2, 3, 4a, 4b, 5a, 5b, and 6 before CAC, and also after CAC at visit 6; slit lamp biomicroscopy at visits 2, 3, 4a, 4b, 5a, 5b, and 6 before CAC, and also after CAC at visit 6 for examination of the anterior chamber, conjunctiva, cornea, eyelid, and lens; intraocular pressure at visits 2 and 6 after CAC; and dilated fundoscopy at visits 2 and 6 after CAC. Once the assigned bilastine or vehicle solutions were instilled, all adverse events reported throughout the rest of the study were considered TEAEs.

The tolerability outcomes were based on a drop comfort assessment using the Drop Comfort Scale (0-10) by patients (upon instillation and 1 and 2 minutes after instillation) following initial dosing at visit 4a and a drop comfort assessment using the Drop Comfort Questionnaire by patients (at 3 minutes after instillation) at visit 4a, with patients choosing 3 of 12 possible words [41,42].

Determination of Sample Size

Assuming an SD of 0.95 units in each treatment arm and a study-wide 2-sided type I error of 0.05 (a familywise 2-sided type I error of 0.0167), a sample size of 28 patients per treatment arm would have 92% power to detect a mean difference of 1.0 unit in ocular itching between bilastine ophthalmic solution–treated and vehicle-treated patients at visit 6. Using the same assumptions, this sample size would have 87% power to show a statistical difference at visits 4b and/or 5b with a Bonferroni-adjusted type I error rate of 0.0083 and conditional upon the analysis at visit 6 showing statistical significance. It was expected that approximately 5% of patients would discontinue the trial prior to completing visit 6.

Statistical Analysis

The primary efficacy analyses were conducted on the intention-to-treat population with last observation carried forward for missing data using analysis of covariance models. Differences between each treatment group and vehicle were calculated as active minus vehicle. Change from baseline was calculated as follow-up visit minus baseline. All statistical tests were 2-sided with a significance level of .05 unless otherwise specified. Two-sample *t* tests were used as unadjusted sensitivity analyses at each post-CAC timepoint.

Comparisons of ocular itching between each dose of bilastine ophthalmic solution and vehicle at visit 6 were made first using a hierarchical testing procedure. If the results for ocular itching at visit 6 (15 minutes after administration) were statistically significant for at least 2 of the 3 timepoints, testing of ocular itching continued for visits 5b (8 hours after

Table 1. Baseline Demographic Characteristics (Intention-to-Treat Population[a]).

	Bilastine 0.2% (n=30)	Bilastine 0.4% (n=30)	Bilastine 0.6% (n=31)	Vehicle (n=30)	All patients (n=121)
Age, y					
Mean (SD)	50.4 (10.7)	47.0 (14.0)	51.8 (13.1)	48.3 (13.2)	49.4 (12.8)
<65 years, No. (%)	28 (93.3)	27 (90.0)	27 (87.1)	27 (90.0)	109 (90.1)
≥65 years, No. (%)	2 (6.7)	3 (10.0)	4 (12.9)	3 (10.0)	12 (9.9)
Sex (male), No. (%)					
Male	14 (46.7)	12 (40.0)	16 (51.6)	13 (43.3)	55 (45.5)
Female	16 (53.3)	18 (60.0)	15 (48.4)	17 (56.7)	66 (54.5)
Ethnicity, No. (%)					
Hispanic or Latino	3 (10.0)	7 (23.3)	4 (12.9)	5 (16.7)	19 (15.7)
Not Hispanic or Latino	27 (90.0)	23 (76.7)	27 (87.1)	25 (83.3)	102 (84.3)

[a]The intention-to-treat population comprised the 121 randomized patients who received their first dose of bilastine at visit 4a.

administration) and 4b (16 hours after administration). If the comparison of ocular itching at visit 6 and at least 1 of visits 5b and 4b was statistically significant, then conjunctival redness was tested according to a similar rationale and following the same hierarchy, albeit with a reduced α level. A Bonferroni adjustment was used to evaluate the different doses of bilastine ophthalmic solution against vehicle to control the study-wide type I error rate at 0.05. Analyses for the secondary efficacy endpoint of conjunctival redness were performed using the same populations and missing data methods as the primary endpoint. Summaries for continuous and ordinal variables included the number of observations, arithmetic mean, and SD. Summaries for discrete variables included frequency counts and percentages.

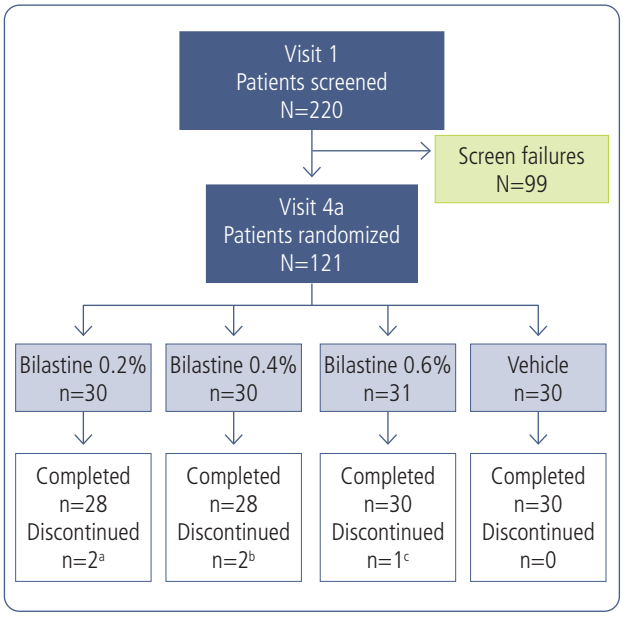

Figure 2. Progress of patients through the trial.
[a]Patients were lost to follow-up.
[b]One patient presented clinically active signs of allergic conjunctivitis at visit 5a; a second patient was lost to follow-up.
[c]Discontinued because of investigator's decision at visit 5a (treatment-emergent adverse effect [hypoesthesia]).

Results

A total of 121 patients (54.5% females and 45.5% males) with a mean (SD) age of 49.4 (12.8) years were randomized (Figure 2). Demographic characteristics are shown in Table 1.

Efficacy

The primary efficacy endpoint in this study was mean reduction in ocular itching. Compared to vehicle, all 3 concentrations of bilastine (0.2%, 0.4%, and 0.6%) showed statistically significant differences in reducing ocular itching ($P<.001$) 15 minutes and 8 and 16 hours after instillation (Figure 3). Mean treatment differences at all post CAC

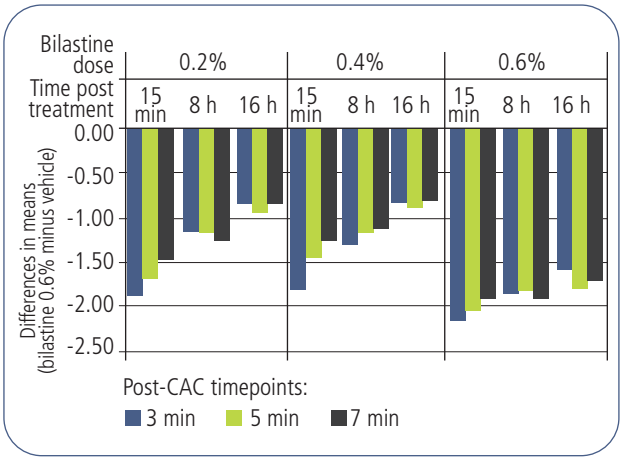

Figure 3. Evaluation of the primary endpoint, ocular itching, at visits 4b (16 hours after treatment), 5b (8 hours), and 6 (15 minutes) by treatment group (treatment differences calculated as bilastine treatment minus vehicle). All differences were significant ($P<.0001$) based on a 2-sample t test comparing the active treatment to the vehicle. CAC indicates conjunctival allergen challenge.

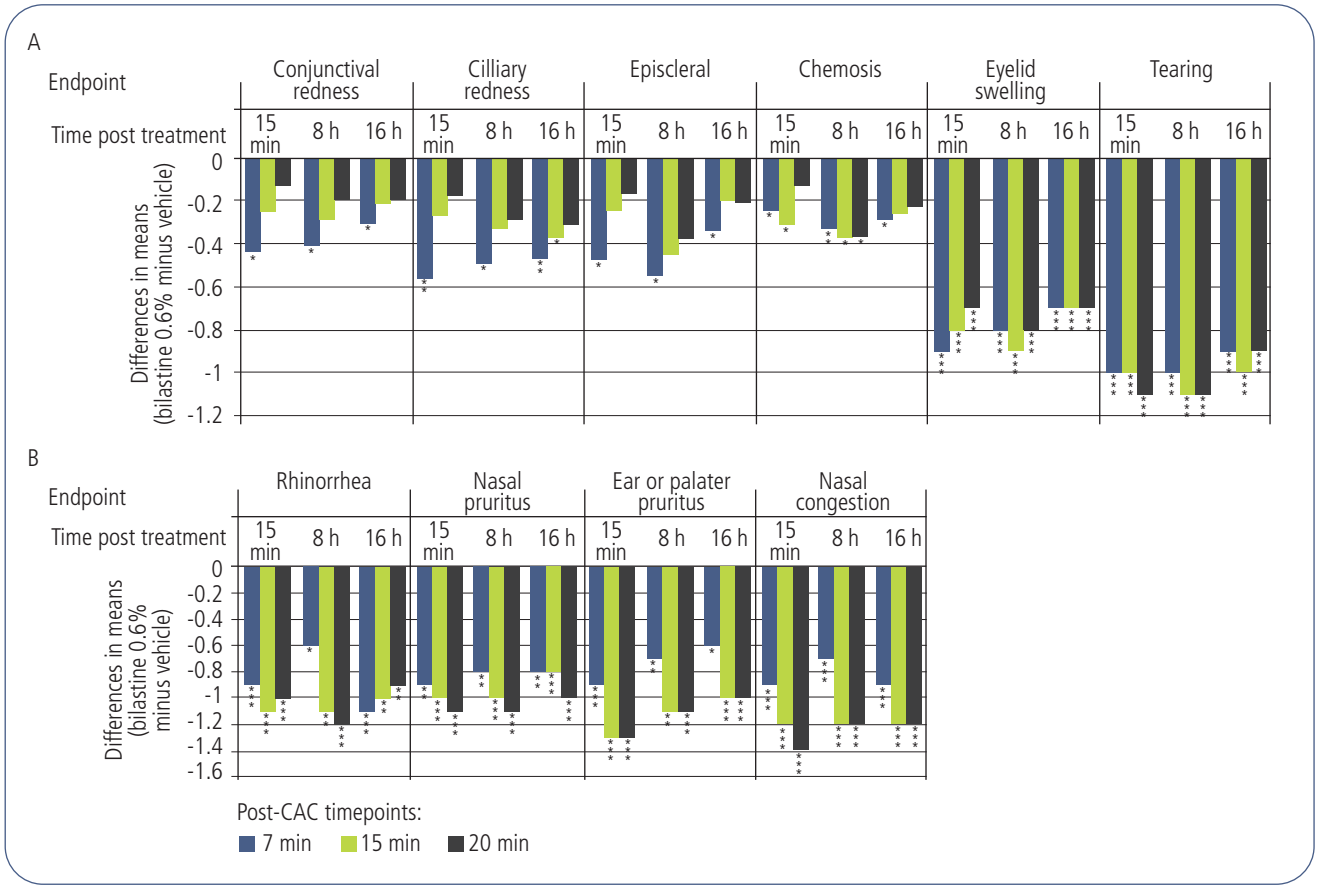

Figure 4. Evaluation of the secondary endpoints at visits 4b (16 hours after treatment), 5b (8 hours), and 6 (15 minutes) for the bilastine 0.6% group. A, Ocular endpoints. B, Nasal endpoints. Treatment differences calculated as bilastine 0.6% minus vehicle. Significance of differences indicated as follows: **P*<.05; ***P*<.01; ****P*<.001. Significance was calculated using a 2-sample *t* test comparing the active treatment to the vehicle. CAC indicates conjunctival allergen challenge.

timepoints were ≥1 unit for bilastine 0.6%. Treatment differences for bilastine 0.2% and 0.4% were ≥1 unit at all post-CAC timepoints 15 minutes and 8 hours after treatment and ≥0.5 units at all timepoints 16 hours after treatment.

For conjunctival redness, statistically significant differences were only recorded for bilastine 0.6% compared to vehicle at most timepoints at all visits (15 minutes, 8 and 16 hours after treatment), while significance was not observed for the 0.4% and 0.2% concentrations at all the visits (Figure 4A).

Treatment differences for bilastine 0.6% were statistically significant (*P*<.001) compared to vehicle at all post-CAC timepoints and at all 3 treatment visits for tearing and eyelid swelling (Figure 4A) and for all 4 nasal symptoms evaluated (rhinorrhea, nasal pruritus, ear or palate pruritus, nasal congestion) (Figure 4B).

In an allergen type analysis, treatment differences between bilastine 0.6% and vehicle were significant (*P*<.001) for ocular itching regardless of allergen type at 15 minutes and at 8 and 16 hours after treatment (Figure 5).

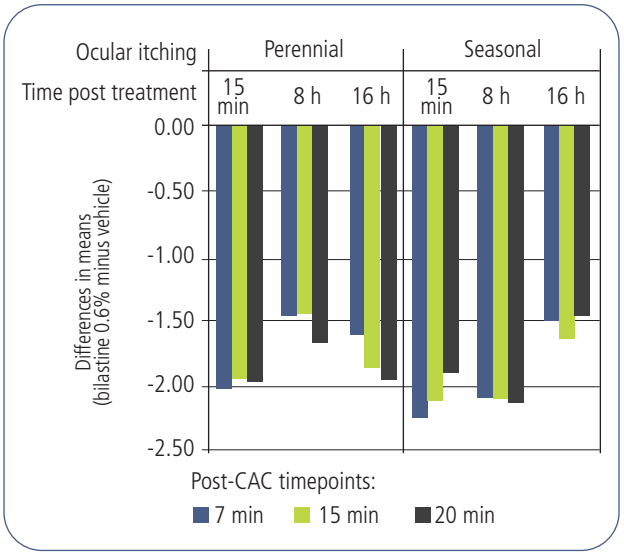

Figure 5. Evaluation of the effects of allergen type on ocular itching at visits 4b (16 hours after treatment), 5b (8 hours), and 6 (15 minutes) for the bilastine 0.6% group. Treatment differences calculated as bilastine 0.6% minus vehicle. Statistical significance in all cases was *P*<.001 based on a 2-sample *t* test comparing the active treatment to the vehicle. CAC indicates conjunctival allergen challenge.

Safety

Nineteen TEAEs were reported by 18 (14.9%) patients (Table 2). A similar number of TEAEs was reported in the bilastine 0.2% group and the vehicle group, with fewer reported

Table 2. Adverse Events (Safety Population).

	Bilastine 0.2% (n=30)	Bilastine 0.4% (n=30)	Bilastine 0.6% (n=31)	Vehicle (n=30)	All patients (n=121)
Number of TEAEs[a]	8	3	1	7	19
Patients with at least 1 TEAE, No. (%)	8 (26.7)	3 (10.0)	1 (3.2)	6 (20.0)	18 (14.9)
Number of ocular TEAEs	5	1	0	2	8
Patients with at least 1 ocular TEAE, No. (%)	5 (16.7)	1 (3.3)	0	2 (6.7)	8 (6.6)
Severity of ocular TEAEs, No. (%)					
Mild	6 (20.0)	2 (6.7)	1 (3.2)	4 (13.3)	13 (10.7)
Moderate	2 (6.7)	1 (3.3)	0	2 (6.7)	5 (4.1)
Eye disorders, No. (%)	4 (13.3)	1 (3.3)	0	2 (6.7)	7 (5.8)
Visual acuity reduced	2 (6.7)	0	0	0	2 (1.7)
Blepharitis	1 (3.3)		0	0	1 (0.8)
Corneal deposits	0	0	0	1 (3.3)	1 (0.8)
Eye discharge	0	0	0	1 (3.3)	1 (0.8)
Keratitis	0	1 (3.3)	0	0	1 (0.8)
Macular fibrosis	1 (3.3)	0	0	0	1 (0.8)
Hordeolum, No. (%)	1 (3.3)	0	0	0	1 (0.8)
Nonocular TEAEs, No. (%)	3	2	1	5	11
Patients with at least 1 nonocular TEAE, No. (%)	3 (10.0)	2 (6.7)	1 (3.2)	5 (16.7)	11 (9.1)
Viral upper respiratory tract infection	1 (3.3)	1 (3.3)	0	3 (10.0)	5 (4.1)
Gastroenteritis	0	0	0	1 (3.3)	1 (0.8)
Headache	0	1 (3.3)	0	0	1 (0.8)
Hypoesthesia	0	0	1 (3.3)	0	1 (0.8)
Pyrexia	1 (3.3)	0	0	0	1 (0.8)
Arthralgia	0	0	0	1 (3.3)	1 (0.8)
Nephrolithiasis	1 (3.3)	0	0	0	1 (0.8)

Abbreviation: TEAE, treatment-emergent adverse event (ie, adverse event reported after the patient received the study drug).
[a]All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0

in the bilastine 0.4% and no ocular TEAEs in the bilastine 0.6% group. Most TEAEs (14/19) were mild in severity, no patients experienced serious AEs, and none of the moderate TEAEs (ocular and nonocular) reported by all the treatment groups were considered related or likely related to treatment.

There were no other general concerns raised by any of the ophthalmic examinations. No patients discontinued the study owing to a related TEAE, and only 1 TEAE was considered related to the study drug (mild headache reported by a patient in the bilastine 0.4% group).

Comfort

Patients reported that all the bilastine ophthalmic solutions were as comfortable as the vehicle ophthalmic solution; all comfort scale scores were low, ranging from 0.60 to 1.08 on the 10-point scale (lower scores indicate more comfort) among all 4 treatment groups (Figure 6A). Patients also more frequently identified the bilastine solution as more "soothing" than the vehicle solution (Figure 6B).

Discussion

This randomized phase 2 clinical trial is the first to compare the efficacy and safety profile of 3 doses of an ophthalmic, preservative-free, formulation of bilastine (0.2%, 0.4%, and 0.6%) with that of its vehicle for the symptomatic treatment of AC. We found that all 3 bilastine concentrations met the primary efficacy endpoint of reducing ocular itching compared to vehicle 15 minutes and 8 hours after treatment and that bilastine 0.6% was also effective 16 hours after treatment. Statistically significant differences were also observed for bilastine 0.6% compared to vehicle in tearing, eyelid swelling, and nasal symptoms at all post-CAC timepoints 16 hours after treatment. The results also showed that bilastine 0.6% was well

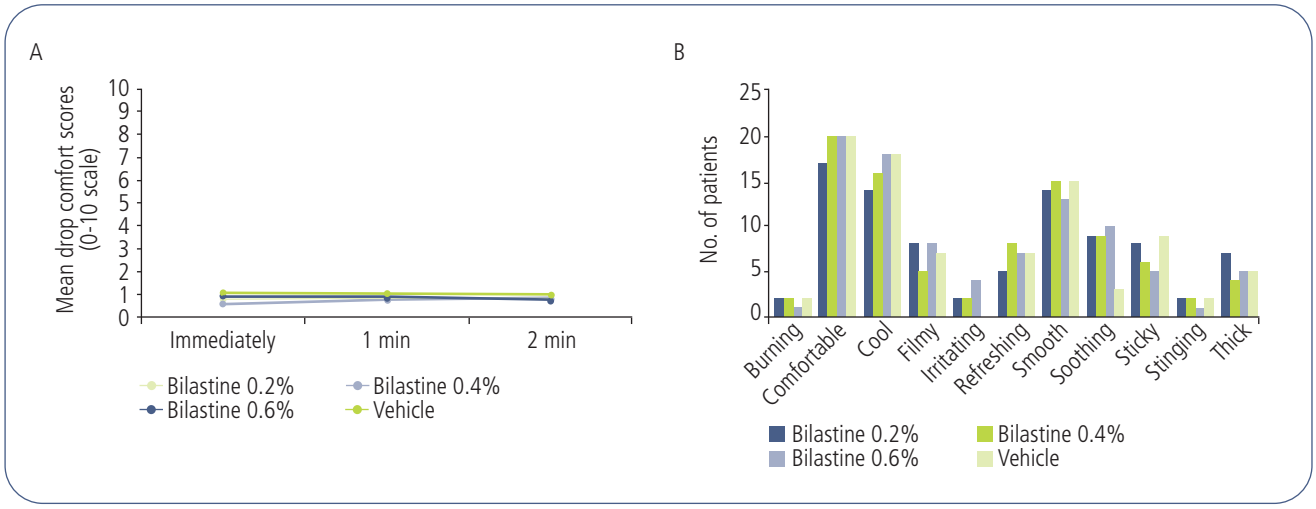

Figure 6. Evaluation of drop comfort. A, Mean drop comfort scores immediately and 1 or 2 minutes after instillation. B, Number of patients reporting specific descriptors of the drops. The Drop Comfort Questionnaire was administered 3 minutes after instillation of the study drug, and participants were asked to choose 3 words that best described how each eye drop feels in both eyes.

tolerated in the range of times tested, and patients reported comfort comparable with that of vehicle.

Ocular itching is the most bothersome symptom reported by patients with AC and greatly affects quality of life [43]. Oral antihistamines, although effective, often have a later local onset of action and the potential for systemic adverse effects. The results reported here show that bilastine 0.6% is efficacious in alleviating ocular itching, with a rapid onset of action (≤15 minutes), combined with a lasting duration of action (≥16 hours). Therefore, once-daily administration of bilastine ophthalmic solution 0.6% may provide relief of ocular symptoms in patients with AC.

Individual secondary signs and symptoms of AC (conjunctival redness, ciliary redness, episcleral redness, chemosis, eyelid swelling, tearing, and nasal symptoms) were measured. Bilastine 0.6% demonstrated statistically significant reductions compared with vehicle in all these symptoms, and for tearing, treatment differences of ≥1.0 units were obtained with bilastine 0.6% even at the 16-hour posttreatment visit. For conjunctival redness, statistically significant differences with respect to vehicle could be observed at the 7-minute timepoint 16 hours after treatment, although the pathophysiology of conjunctival redness is not directly targeted by antihistamines [44].

An analysis of allergen type (seasonal or perennial) revealed significant differences between bilastine 0.6% and vehicle (P<.001) for ocular itching regardless of allergen type at 15 minutes and 8 and 16 hours after treatment (Figure 5), with differences at all post-CAC timepoints ≥1 unit in favor of bilastine 0.6%. Oral bilastine had previously been shown to be effective in treating seasonal and perennial allergic rhinoconjunctivitis [14,15,17], and the results presented here suggest that the ophthalmic bilastine formulation is effective for the treatment of AC.

This study also assessed the safety of the bilastine ophthalmic formulation. After the review of AEs and ocular safety parameters, no safety concerns were identified for bilastine 0.6% after once-daily dosing for 3 nonconsecutive days in adults with AC. Additionally, patients reported that the bilastine ophthalmic solutions were as comfortable as the vehicle ophthalmic solution and frequently described the bilastine 0.6% ophthalmic formulation as the most soothing.

A number of antihistamine ophthalmic solutions have been developed in the last decade [45-50]; however, there remains a need for comparative studies to investigate their relative efficacy [51]. In this regard, the results of a phase 3 clinical trial comparing bilastine 0.6%, ketotifen 0.025%, and vehicle will be published shortly.

In conclusion, the present study shows that bilastine 0.6% is superior to its vehicle for the treatment of ocular itching at the onset of action and has at least a 16-hour duration of action, supporting once-daily administration with good tolerability. Patients considered the preservative-free bilastine formulation highly comfortable. Bilastine 0.6% ophthalmic formulation constitutes a new once-daily topical therapeutic option for the symptomatic treatment of AC.

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Conflicts of Interest

PJG is an employee of Ora Inc. (Andover, Massachusetts, USA). GH, PA, and NF are employees of FAES FARMA (Bizkaia, Spain). JBC is a consultant to Ora Inc.

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