ORIGINAL ARTICLE

# Bilastine 0.6% Preservative-free Eye Drops: A Once-daily Treatment for Allergic Conjunctivitis

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J Investig Allergol Clin Immunol 2024; Vol. 34(3): 167-176
doi: 10.18176/jiaci.0894

## Abstract

*Background:* Bilastine is a second-generation antihistamine approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. The present trial evaluated the efficacy and safety of a new bilastine 0.6% preservative-free eye drop formulation for the symptomatic treatment of allergic conjunctivitis.
*Methods:* This phase 3, multicenter, double-masked, randomized study compared the efficacy, safety, and tolerability profile of bilastine 0.6% ophthalmic solution with that of ketotifen 0.025% and vehicle. The primary efficacy endpoint was reduction in ocular itching. The Ora-CAC® Allergen Challenge Model was used to assess ocular and nasal symptoms at 15 minutes (onset of action) and 16 hours after treatment.
*Results:* Patients (N=228) were 59.6% male, and the mean (SD) age was 44.1 (13.4) years. Bilastine demonstrated efficacy in reducing ocular itching compared to vehicle at both onset of action and 16 hours after treatment ($P<.001$). Symptoms improved with ketotifen compared to vehicle 15 minutes after treatment ($P<.001$). Bilastine demonstrated statistical noninferiority to ketotifen for all 3 post-CAC timepoints at 15 minutes after instillation, based on an inferiority margin of 0.4. Compared with vehicle, bilastine improved in conjunctival redness, ciliary redness, episcleral redness, chemosis, eyelid swelling, tearing, rhinorrhea, ear and palate pruritus, and nasal congestion at 15 minutes after treatment ($P<.05$). Ophthalmic bilastine was safe and well tolerated. Mean drop comfort scores were significantly better for bilastine than for ketotifen immediately upon instillation ($P<.05$) and similar to those of vehicle.
*Conclusions:* Ophthalmic bilastine effectively reduced ocular itching for 16 hours after administration, suggesting that it could be used as a once-daily treatment for the signs and symptoms of allergic conjunctivitis. ClinicalTrials.gov identifier: NCT03479307.

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

## Resumen

*Antecedentes*: La bilastina es un antihistamínico de segunda generación aprobado para el tratamiento sintomático de la rinoconjuntivitis alérgica y la urticaria. Este ensayo evaluó la eficacia y seguridad de una nueva formulación de colirio de bilastina al 0,6% sin conservantes para el tratamiento sintomático de la conjuntivitis alérgica.
*Métodos:* Este estudio de fase 3, multicéntrico, doble enmascarado y aleatorizado evaluó la eficacia, seguridad y tolerabilidad de bilastina 0,6% solución oftálmica en comparación con ketotifeno 0,025% y vehículo. El criterio principal de eficacia fue la reducción del picor ocular. Se utilizó el modelo de provocación con alérgeno Ora-CAC® para evaluar los síntomas oculares y nasales a los 15 minutos (inicio de la acción) y a las 16 horas después del tratamiento.
*Resultados:* El 59,6% de los sujetos (N=228) eran varones y la edad media (DE) era de 44,1 (13,4) 15 años. La bilastina demostró eficacia en la reducción del prurito ocular en comparación con el vehículo tanto al inicio de la acción como 16 horas después del tratamiento ($p<0,001$). El ketotifeno mostró mejoría en comparación con el vehículo 15 minutos después del tratamiento ($p<0,001$). Bilastina demostró no inferioridad estadística con respecto al ketotifeno en los 3 puntos temporales posteriores al CAC a los 15 minutos después de la instilación, con un margen de inferioridad de 0,4. La bilastina demostró mejoría sobre el vehículo ($p<0,05$) para el enrojecimiento conjuntival, enrojecimiento ciliar, enrojecimiento epiescleral, quemosis, hinchazón de párpados, lagrimeo, rinorrea, prurito de oídos y paladar, y congestión nasal a los 15 minutos del tratamiento. La bilastina oftálmica fue segura y bien tolerada. Las puntuaciones medias de aceptación de la gota fueron significativamente mejores ($p<0,05$) para bilastina en comparación con ketotifeno inmediatamente después de la instilación, y similares en comparación con el vehículo.
*Conclusiones:* La bilastina oftálmica redujo eficazmente el prurito ocular durante las 16 horas posteriores al tratamiento, lo que sugiere que podría utilizarse como tratamiento una vez al día para los signos y síntomas de la conjuntivitis alérgica. Identificador de ClinicalTrials.gov: NCT03479307.

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

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**Summary box**

- **What do we know about this topic?**
  Bilastine is a second-generation antihistamine approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. A new preservative-free eye drop formulation of bilastine 0.6% for the symptomatic treatment of allergic conjunctivitis has been developed and evaluated.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  This study demonstrates that the new ophthalmic bilastine 0.6% formulation could be used as once-daily treatment for the signs and symptoms of allergic conjunctivitis.

## Introduction

Allergic conjunctivitis (AC) is an inflammatory process that can result from an IgE-mediated hypersensitivity reaction caused by direct contact between an allergen and the conjunctiva. It affects about 40% of the population, and its incidence appears to be increasing, as is the case for other allergic conditions [1]. AC generally affects both eyes, and patients report symptoms such as conjunctival pruritus (most bothersome symptom), tearing, and a burning or stinging sensation. Blurred vision and photophobia can occur in the most severe cases. Clinical signs such as conjunctival hyperemia or injection (red eyes) are observed, as are moderate conjunctival and eyelid edema (swollen eyes). These symptoms can significantly impact patients' quality of life [2,3]. Treatment of AC includes ophthalmic antihistamines, mast cell stabilizers, dual action agents, and corticosteroids. Most available multidose ophthalmic treatments contain preservative compounds that contribute to ocular surface toxicity [4,5]. Moreover, since adherence decreases when several daily instillations are required, a single dose is preferred [5]. Therefore, single-dose preservative-free eye drops should be used to minimize possible toxic effects of preservatives on the ocular surface and ensure adherence. To address these unmet needs, a multidose, once-daily, preservative-free bilastine ophthalmic solution has been developed.

Bilastine is a second-generation nonsedating H1 antihistamine approved for oral symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children [6]. The efficacy of oral bilastine in reducing ocular symptoms in patients with allergic rhinoconjunctivitis has been extensively demonstrated in clinical trials [7-11]. Characterization of safety and tolerability in children aged 2 to 11 years, adolescents, adults, and elderly patients has revealed a good safety profile [12-15].

Preclinical in vivo biodistribution and pharmacokinetic studies in humans have shown that the ophthalmic formulation of bilastine is most concentrated on the conjunctiva, the intended target tissue, while drug absorption into the bloodstream is minimal [16,17]. A recent dose-finding study in adults showed that the bilastine 0.6% ophthalmic formulation rapidly reduces ocular itching and that this effect is maintained for 16 hours after treatment, making it suitable for once-daily administration [18]. Bilastine 0.6% ophthalmic solution was also more efficient than vehicle for controlling tearing, eyelid swelling, and nasal symptoms [18].

The primary objective of the present phase 3 study was to compare the efficacy of the ophthalmic bilastine 0.6% formulation with that of its vehicle and an ophthalmic multidose formulation of ketotifen 0.025% (Zaditen, Laboratoires Théa) [19], a dual-action agent for the treatment of the signs and symptoms of AC. Safety and tolerability were also investigated. To carry out this research, the drugs were assessed following the Ora-CAC® Allergen Challenge Model (CAC hereinafter), which is a well-established and standardized methodology for evaluating drugs intended to treat AC [20,21]. This model was specifically designed to mimic the signs and symptoms of ocular allergy in a precise and consistent manner, reproducing what occurs in AC in a controlled clinical setting in which external and internal factors are minimized. Applying CAC to assess AC allows for a high degree of reproducibility and internal control and is the first clinical disease model accepted by the United States Food and Drug Administration for the approval of new drugs. This methodology is also recommended by the European Academy of Allergy and Clinical Immunology and the Japanese Pharmaceuticals and Medical Devices Agency [22].

## Methods

We performed a multicenter, double-masked, randomized, vehicle- and active-controlled, phase 3 CAC study to compare the efficacy and safety profile of ophthalmic bilastine 0.6% with that of ketotifen 0.025% and vehicle for the treatment of AC. The study was carried out at 6 ophthalmology clinics in the US between April 7, 2018 (first patient enrolled) and August 10, 2018 (last patient, last visit).

Participants provided their written informed consent before undergoing any study-related procedures. The study was performed in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, the protocol, the ICH guideline on Good Clinical Practice (GCP), and all applicable local regulatory requirements and laws.

### *Study Design*

The efficacy of ophthalmic bilastine 0.6% and ketotifen 0.025% was evaluated using CAC [20]. The methodology has been described in detail before, and a scheme of activities carried out at each visit is summarized in Figure 1 and Supplementary Figure 1. At the screening visit (visit 1), patients signed


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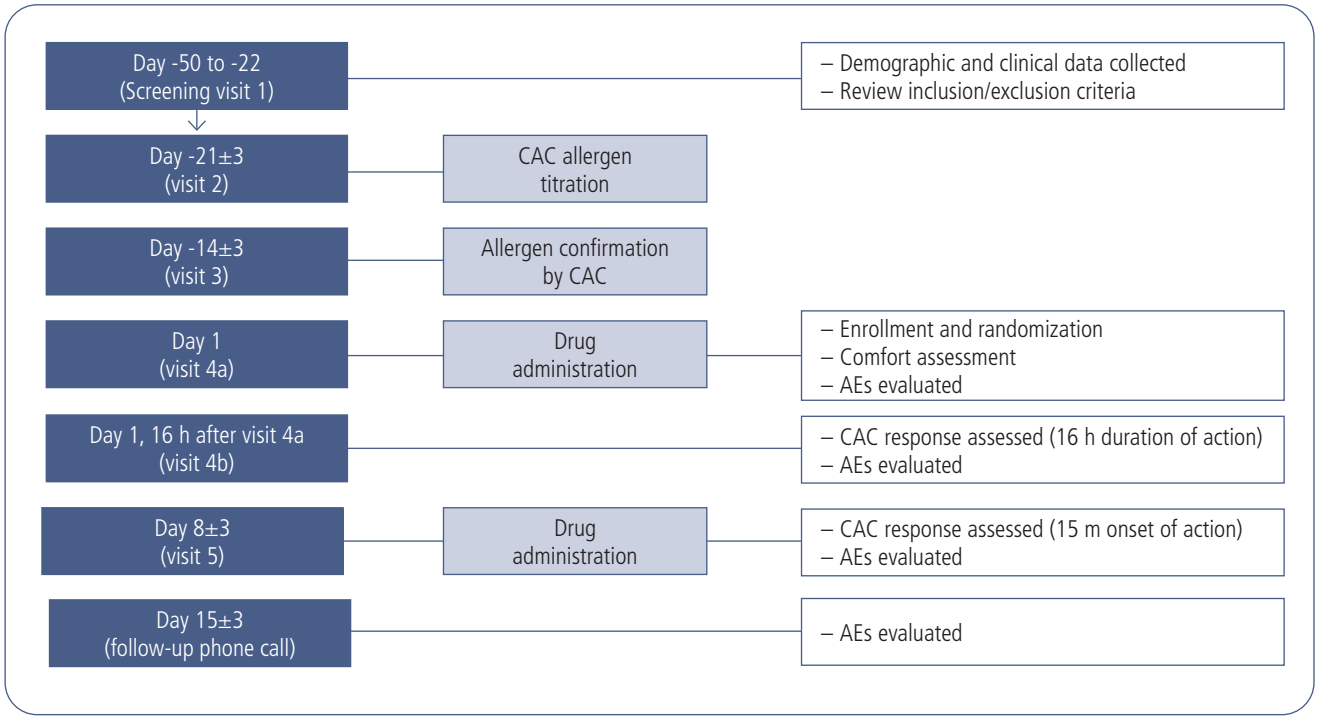


**Figure 1.** Study design according to the Ora-CAC® Allergen Challenge Model.
Abbreviations: AEs, adverse events; CAC, conjunctival allergen challenge.

the informed consent, demographic data and a medical and medication history were acquired, and inclusion and exclusion criteria were reviewed. At visit 2, a titration CAC was performed bilaterally with a perennial or seasonal allergen administered via micropipette. Patients received 1 drop of a solubilized allergen in each eye at the weakest dilution to which they were sensitized. If the patient failed to react within 10 (±2) minutes, increasingly concentrated doses were instilled bilaterally at approximately 10-minute intervals until a positive 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 same concentration identified at visit 2. Patients with a positive bilateral CAC reaction were considered qualifying patients. A positive CAC response at visit 2 was defined as a score of ≥2 for itching and ≥2 for redness in the conjunctival vessel bed in each eye within 10 minutes of receiving the allergen dose.

At visit 3, a confirmation CAC was conducted, with each qualified patient receiving 1 drop of the allergen solution bilaterally at the same final dose that elicited a positive reaction at visit 2. Ocular and nasal allergic signs and symptoms were assessed after CAC.

At visit 4a, patients were randomized at a 2:2:1 ratio to 1 of the 3 treatment groups (bilastine, ketotifen, or vehicle, respectively). A trained study technician instilled the assigned drug or vehicle 16 (±1) hours before performing CAC at visit 4b. Patients were asked to rate the comfort of the treatment administered in each eye using the Ora Calibra® Drop Comfort Scale. They also described how the treatments felt in each eye using the Ora Calibra Drop Comfort Questionnaire.

At visit 4b, 16 (±1) hours after instillation, each patient received 1 drop of the allergen solution bilaterally at the same final 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 using the Ora Calibra® scales.

At visit 5 (day 8±3), the assigned product was instilled again in each patient by a trained study technician 15 (+1) minutes before CAC. A CAC was conducted, with each patient receiving 1 drop of the allergen solution bilaterally to assess onset of action.

At day 15 (±3), the investigator telephoned all patients to inquire whether there were any changes in their medical history or medications, adverse events (AEs), emergency room visits, or hospitalizations since their previous study visit.

AEs were evaluated at each visit and considered treatment-emergent adverse events (TEAEs) once patients had received the first study drug.

### *Patient Population*

The inclusion criteria were as follows: age ≥18 years; 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 a score of ≥2 for ocular itching and ≥2 for 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 time points following challenge at visit 3; calculated visual acuity of 0.7 logMAR or better in each eye, as measured using an ETDRS chart; and informed consent.

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The exclusion criteria were as follows: contraindications or sensitivity to the use of bilastine, ketotifen, or vehicle; any ocular condition that, in the investigator's 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); a known history of retinal detachment, diabetic retinopathy, or active retinal disease; taking any of the disallowed medications during the period indicated prior to the first CAC at visit 2 and during the study period (systemic antihistamines, decongestants, monoamine oxidase inhibitors, all topical ophthalmic preparations, lid scrubs, prostaglandins, nonsteroidal anti-inflammatory drugs, corticosteroids); 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); and significant illness that the investigator felt could be expected to interfere with the patient's health or with the study parameters. Female volunteers who were pregnant, planning a pregnancy, or breastfeeding were also excluded; females of childbearing potential were required to have a negative pregnancy test result at screening and to use an acceptable birth control method during the study.

### *Treatments and Assessments*

Ophthalmic bilastine 0.6% was supplied by FAES Farma, and ketotifen multidose ophthalmic solution 0.025% (Zaditen) was acquired from Laboratoires Théa. Ketotifen ophthalmic solution vehicle was provided by FAES Farma. All selected products were in multidose containers. At the time of the study, preservative-free multidose ketotifen was not available; therefore, multidose ketotifen with preservatives was selected.

Ocular itching, the primary efficacy outcome, was evaluated by the patient at 3 (±1), 5 (±1), and 7 (±1) minutes after CAC, which was performed 16 hours after drug instillation at visit 4b (16-hour duration of action) and 15 minutes after drug instillation at visit 5 (15-minute onset of action). Ocular itching was assessed using a 0 to 4 Ora Calibra® Ocular Itching Scale, where 0=none and 4=very severe. Secondary efficacy outcomes such as conjunctival, ciliary, and episcleral redness and chemosis evaluated by the investigator and eyelid swelling, tearing, rhinorrhea, nasal, ear or palate pruritus, and nasal congestion assessed by the patient were evaluated at 7 (±1), 15 (±1), and 20 (±1) minutes after CAC at visits 4b and 5 (Supplementary Methods). The safety variables monitored during the study were those routinely captured to monitor ocular health in a clinical study of allergy. The incidence of TEAEs (ocular and nonocular TEAEs scored separately) during the study was the key safety variable (Supplementary Methods).

The tolerability outcomes were as follows: patient assessment of drop comfort upon instillation and at 1 and 2 minutes after the first study drug instillation using the Ora Calibra Drop Comfort Scale (0-10, a lower score indicates greater comfort); and patient assessment of drop comfort at 3 minutes after instillation using the Ora Calibra Drop Comfort Questionnaire, with patients choosing 3 out of 12 possible words (burning, comfortable, cool, filmy, gritty, irritating, refreshing, smooth, soothing, sticky, stinging, and thick).

### *Determination of Sample Size*

A total of 225 patients were to be randomized at visit 4a at a ratio of 2:2:1 across the 3 treatment arms (90 to bilastine 0.6%; 90 to ketotifen 0.025%; 45 to vehicle). Approximately 5% of patients were expected to discontinue the trial before completing visit 5.

Assuming a treatment difference of 1.25 units, an SD of 0.90 units, and a 2-sided type I error of 0.05, 90 patients in the bilastine treatment arm and 45 patients in the vehicle treatment arm would have provided a >99.9% power to demonstrate a statistically significant difference in ocular itching between bilastine- and vehicle-treated patients at each primary post-CAC time point (3 [±1], 5 [±1], and 7 [±1] minutes) at visit 4b or visit 5. Additionally, assuming independence between the time points, this sample size would have at least a 99.4% power to demonstrate a statistically significant difference between bilastine- and vehicle-treated patients at all primary post-CAC time points for ocular itching at visits 4b or 5.

Ninety patients in the bilastine treatment group and 90 patients in the ketotifen treatment group yielded a 96% power to reject the null hypotheses corresponding to the noninferiority test for ocular itching ($H_{20}$) for a single time point. This calculation assumed a noninferiority margin of $\Delta$=0.40, a 1-sided significance level of 0.025, an actual treatment difference of 0.10 in favor of bilastine, and an SD of 0.90 units. Furthermore, the same sample size and assumptions yielded an 88.5% power to show that bilastine was noninferior to ketotifen in terms of ocular itching scores for all 3 time points at visit 5. In this study, ketotifen was administered as a single dose, with the objective of comparing efficacy at the onset of action at visit 5.

Considering that ketotifen should be administered twice daily, no comparison with bilastine or vehicle was made at visit 4b (16 hours).

Ninety patients in the ketotifen treatment group and 45 patients in the vehicle treatment group yielded a >99.9% power to reject $H_{30}$ for a single time point (no difference in ocular itching between ketotifen- and vehicle-treated patients). This calculation assumed a 2-sided significance level of 0.05, a treatment difference of 1.1 units, and an SD of 0.90 units. Additionally, this sample size would have a 99.4% power to demonstrate a statistically significant difference at all primary post-CAC time points at visit 5 for ocular itching between ketotifen- and vehicle-treated patients, assuming independence between time points.

### *Statistical Methods*

Statistical programming and analyses were performed using SAS® Version 9.4. Missing data for the primary efficacy variable and for the secondary efficacy variable of conjunctival redness were imputed using a variety of techniques: multiple imputations using Markov chain Monte Carlo, last observation carried forward, and multiple imputations made on a control-based pattern mixture model.

Differences between each treatment group and vehicle were calculated as active minus vehicle. Change from baseline was calculated as follow-up visit minus baseline.


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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 time point. Summaries for continuous and ordinal variables included the number of observations, arithmetic mean, and SD. Summaries for discrete variables included frequency counts and percentages.

## Results

A total of 228 patients were randomized to the 3 study groups (Supplementary Figure 1). Their demographic characteristics are shown in Table 1. The population was 59.6% male, and the mean (SD) age was 44.1 (13.4) years.

### *Primary Efficacy Endpoint*

Ocular itching was self-assessed by patients in each eye at 15 minutes and 16 hours after instillation of the study medication and at 3, 5, and 7 minutes after CAC. The bilastine-treated group demonstrated statistically significant ($P<.001$) efficacy in reducing ocular itching compared to the vehicle group at all time points at both 15 minutes and 16 hours after treatment (Figure 2). The ketotifen group showed statistically significant improvements compared with vehicle at all 3 post-CAC time points 15 minutes after treatment. Comparison of the bilastine and ketotifen groups demonstrated that bilastine was statistically noninferior at all 3 post-CAC time points 15 minutes after instillation of the study medication, based on an inferiority margin of 0.4.

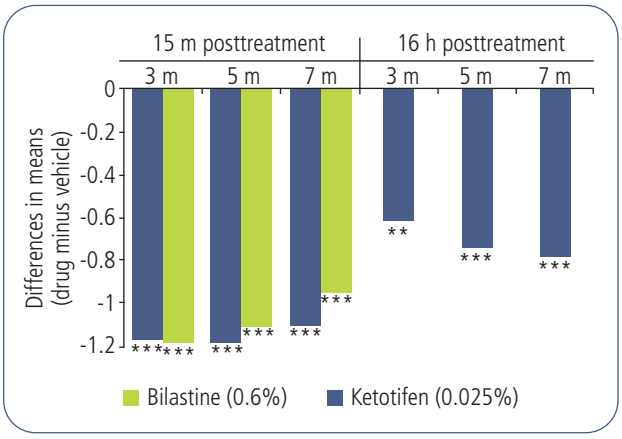


**Figure 2.** Evaluation of ocular itching 15 minutes after treatment and 16 hours after treatment in patients treated with bilastine 0.6% and ketotifen 0.025%. Each eye was assessed using a 5-point scale (0-4, half units allowed) at visit 5 (15 minutes after instillation of study medication) and visit 4b (16 hours after instillation of study medication) at 3, 5, and 7 minutes after CAC. Values are indicated as differences in the means of drug minus vehicle. Statistical significance is indicated as follows: **, $P<.001$; ***, $P<.0001$.

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

| Variable | Bilastine (n=91) | Ketotifen (n=90) | Vehicle (n=47) | All patients (N=228) |
|---|---|---|---|---|
| Age, y | | | | |
| Mean (SD) | 45.9 (12.9) | 41.7 (12.1) | 45.1 (16.0) | 44.1 (13.4) |
| <65 y, No. (%) | 85 (93.4) | 89 (98.9) | 43 (91.5) | 217 (95.2) |
| ≥65 y, No. (%) | 6 (6.6) | 1 (1.1) | 4 (8.5) | 11 (4.8) |
| Sex, No. (%) | | | | |
| Male | 58 (63.7) | 53 (58.9) | 25 (53.2) | 136 (59.6) |
| Female | 33 (36.3) | 37 (41.1) | 22 (46.8) | 92 (40.4) |
| Ethnicity, No. (%) | | | | |
| Hispanic or Latino | 11 (12.1) | 10 (11.1) | 6 (12.8) | 27 (11.8) |
| Not Hispanic or Latino | 80 (87.9) | 79 (87.8) | 41 (87.2) | 200 (87.7) |
| Unknown | 0 | 1 (1.1) | 0 | 1 (0.4) |
| Allergic comorbidities, No. (%) | | | | |
| Allergic rhinitis | 66 (72.5) | 62 (68.9) | 31 (66.0) | 159 (69.7) |
| Allergic pharyngitis | 56 (61.5) | 52 (57.8) | 26 (55.3) | 134 (58.8) |
| Asthma | 3 (3.3) | 3 (3.3) | 1 (2.1) | 7 (3.0) |
| Food allergy | 5 (5.5) | 3 (3.3) | 0 | 8 (3.5) |
| Drug hypersensitivity | 1 (1.1) | 3 (3.3) | 1 (2.1) | 5 (2.2) |
| Contact dermatitis | 1 (1.1) | 0 | 0 | 1 (0.4) |
| Eczema | 1 (1.1) | 0 | 0 | 1 (0.4) |

[a]The intention-to-treat population comprised the 228 randomized patients who received their first dose of bilastine at visit 4a.

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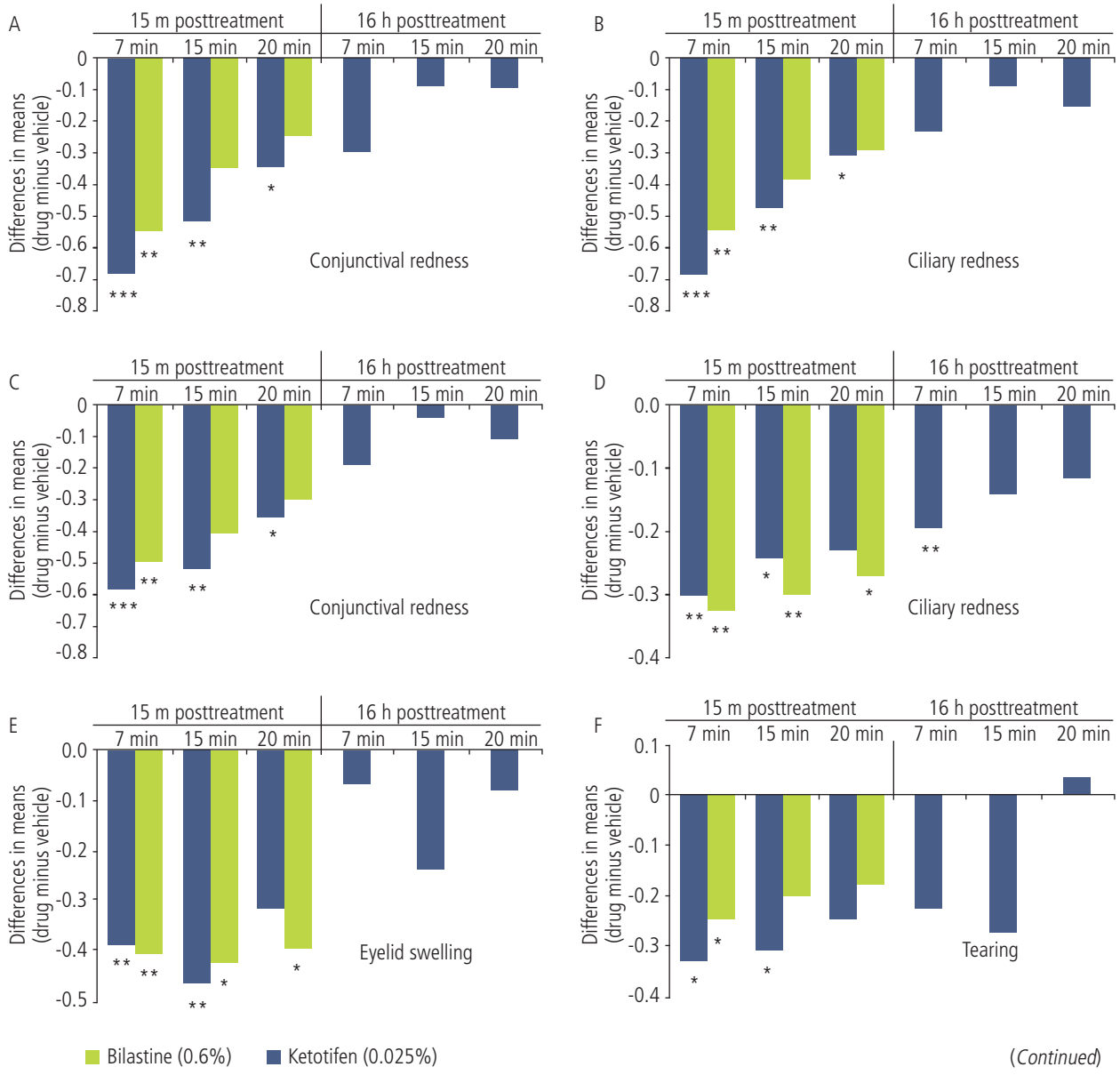
### *Secondary Efficacy Endpoints*

For the secondary endpoint, conjunctival redness, treatment differences were statistically significant ($P<.05$) for bilastine 0.6% compared with vehicle at all time points 15 minutes after instillation (Figure 3A). However, no statistically significant differences in treatment were observed for bilastine compared with vehicle 16 hours after treatment ($P=.0663$, $P=.5933$, and $P=.5850$ for the 7-, 15-, and 20-minute time points, respectively). The noninferiority test between bilastine and ketotifen demonstrated significant $P$ values at all 3 time points at visit 5 (onset of action), indicating that bilastine was noninferior to ketotifen based on a noninferiority margin of 0.4 ($P<.0001$ for all time points).

Furthermore, mean treatment differences for bilastine were statistically significant ($P<.05$) compared to vehicle at most post-CAC time points 15 minutes after treatment for other secondary efficacy endpoints: ciliary redness ($P<.0001$), episcleral redness ($P<.0001$), chemosis ($P=.0014$), eyelid swelling ($P=.0008$), tearing ($P=.0074$), rhinorrhea ($P=.0007$), nasal pruritus ($P=.0219$), ear or palate pruritus ($P=.0066$), and nasal congestion ($P=.0011$) (Figure 3).

Bilastine was associated with significant $P$ values in the noninferiority test at the onset of action for ciliary and episcleral redness, chemosis, eyelid swelling, tearing, rhinorrhea, ear and palate pruritus, and nasal congestion, indicating that it is noninferior to ketotifen based on a noninferiority margin of 0.4 (Figure 3).

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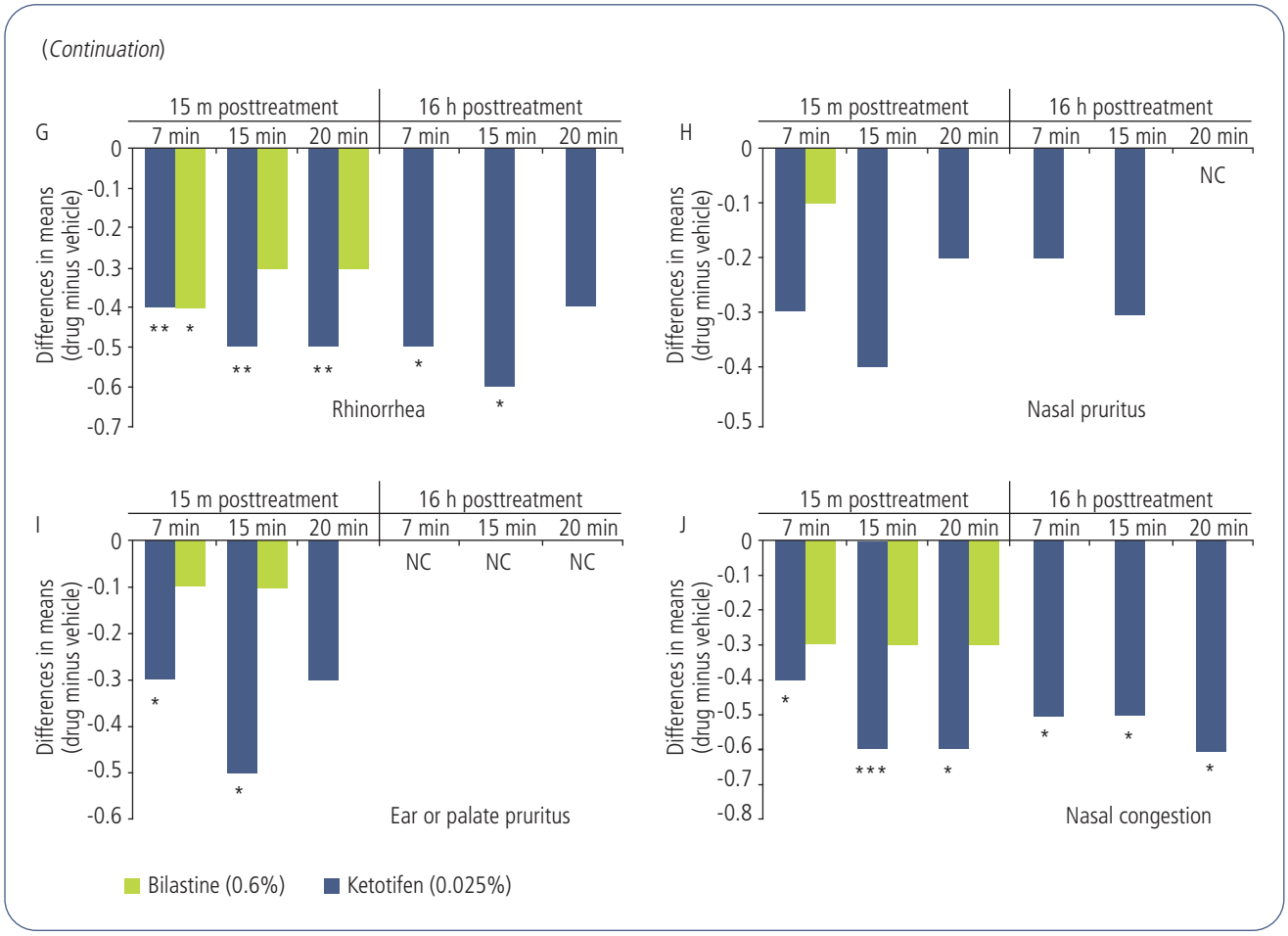


**Figure 3.** Evaluation of secondary endpoints. Each eye was assessed using a 5-point scale (0-4, half units allowed) at visit 5 (15 minutes after instillation of study medication) and visit 4b (16 hours after instillation of study medication) at 7, 15, and 20 minutes after conjunctival allergen challenge. A, Conjunctival redness; B, Ciliary redness; C, Episcleral redness; D, Chemosis; E, Eyelid swelling; F, Tearing; G, Rhinorrhea; H, Nasal pruritus; I, Ear or palate pruritus; J, Nasal congestion. Statistical significance is indicated as follows: *, $P<.05$; **, $P<.001$; ***, $P<.0001$. Abbreviation: NC, no change.

### *Safety*

A total of 7 TEAEs were reported in the safety population: 4 in the bilastine treatment group, 2 in the ketotifen group, and 1 in the vehicle group (Table 2). Five were ocular adverse events, 3 reported by patients treated with bilastine and 2 in the ketotifen group. The most frequently reported was reduction in visual acuity (3 cases), followed by conjunctivitis and hordeolum, with 1 case each. All TEAEs reported were mild in severity and, after assessment of causality, none were considered related to the study medication. No other general concerns were raised by any of the ophthalmic examinations.

### *Tolerability*

The mean drop comfort scores self-reported immediately upon instillation by patients in the bilastine group were significantly lower ($P<.05$) than the mean in the ketotifen group (lower score indicating greater comfort). Mean drop comfort scores in the bilastine group were as follows: 0.76 immediately after instillation of the study medication, 0.79 at 1 minute after instillation, and 0.78 at 2 minutes after instillation. In the ketotifen group, the mean drop comfort scores were 1.52, 1.08, and 0.95 immediately, 1 minute, and 2 minutes after instillation, respectively.

A statistically significant difference in drop comfort immediately upon instillation was reported between the bilastine treatment group and the ketotifen group ($P=.0003$), indicating that bilastine was significantly more comfortable than ketotifen. However, no statistically significant differences in drop comfort were recorded between the bilastine treatment group, the ketotifen group, and the vehicle group at 1- and 2-minutes after instillation (Figure 4A).

Regarding the Ora Calibra Drop Comfort Questionnaire, the assessment was performed 3 minutes after instillation, and responses were similar between the 3 treatment groups. Bilastine and ketotifen presented similar profiles overall, although more patients selected the terms ‘smooth’ and ‘soothing’ for the bilastine formulation than for ketotifen.

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**Table 2.** Adverse Events (Safety Population, N=228).[a]

| | Bilastine (n=91) | Ketotifen (n=90) | Vehicle (n=47) | All patients (N=228) |
|---|---|---|---|---|
| TEAEs, No. | 4 | 2 | 1 | 7 |
| Patients with at least 1 TEAE, No. (%) | 4 (4.4) | 1 (1.1) | 1 (2.1) | 6 (2.6) |
| Ocular TEAEs, No. | 3 | 2 | 0 | 5 |
| Patients with at least 1 ocular TEAE, No. (%) | 3 (3.3) | 1 (1.1) | 0 | 4 (1.8) |
| Severity of ocular TEAEs, No. (%) | | | | |
| Mild | 3 (3.3) | 1 (1.1) | 0 | 4 (1.8) |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| Eye disorders, No. (%) | | | | |
| Visual acuity reduced | 3 (3.3) | 0 | 0 | 3 (1.3) |
| Conjunctivitis | 0 | 1 (1.1) | 0 | 1 (0.4) |
| Hordeolum | 0 | 1 (1.1) | 0 | 1 (0.4) |
| Nonocular TEAEs, No. (%) | 1 | 0 | 1 | 2 |
| Patients with at least 1 nonocular TEAE, No. (%) | 1 (1.1) | 0 | 1 (1.1) | 2 (0.9) |
| Sinusitis | 1 (1.1) | 0 | 0 | 1 (0.4) |
| Tooth abscess | 0 | 0 | 1 (2.1) | 1 (0.4) |

[a]n in the headers represents the total number of patients in each respective treatment group within the safety population and is used as the denominator for calculating percentages. A TEAE is defined as an AE that occurred after the first dose of study medication. All TEAEs were coded using the Medical Dictionary for Regulatory Activities, Version 20.1

Abbreviation: TEAE, treatment-emergent adverse event.

A burning sensation was selected by 3% of the patients in the ketotifen group, but only by 1% in the bilastine group.

## Discussion

This phase 3 randomized clinical trial compared the efficacy, safety, and tolerability profile of a newly developed ophthalmic formulation of bilastine for the relief of signs and symptoms of AC with that of ketotifen and vehicle. The results showed that bilastine 0.6% achieved the primary efficacy endpoint of reduction in ocular itching both at 15 minutes (onset of action) and 16 hours after instillation. Additionally, bilastine was noninferior to ketotifen at onset of action. Regarding secondary efficacy endpoints, the differences between bilastine and vehicle were statistically significant at onset of action for conjunctival redness, ciliary redness, episcleral redness, eyelid swelling, tearing, ear and palate pruritus, and nasal congestion and proved to be noninferior to multidose ketotifen. Moreover, the bilastine ophthalmic formulation was reported to be significantly more comfortable. No safety concerns were detected during the trial, and bilastine was well tolerated. The overall results suggest that the multidose once-daily bilastine 0.6% formulation is an efficacious and safe preservative-free topical antihistamine formulation for alleviating ocular itching in patients with AC.

The hallmark symptom of AC is ocular itching, which can range from mildly noticeable to debilitating in severity. Topical dual-activity agents are often used as first-line therapy in AC because of their ability to reduce symptoms and improve tolerability [3,5]. Most topical treatments, even those with dual-acting agents, require repeated daily administration, contributing to lack of adherence and, consequently, suboptimal control of AC symptoms [23,24]. Additionally, formulations containing preservatives contribute to a burning sensation that may have a negative impact on adherence. The CAC model described here demonstrated the immediate efficacy of bilastine after administration and that the duration of action of bilastine 0.6% was at least 16 hours after instillation, confirming that the drug could be used as once-daily treatment for AC. In this study, the bilastine 0.6% ophthalmic formulation was compared with the ketotifen multidose ophthalmic solution 0.025% (Zaditen), a dual-activity agent with antihistamine and mast cell–stabilizing activity. The Zaditen multidose formulation contains benzalkonium chloride 0.1 mg/mL, a surfactant preservative that has been shown to induce ocular surface toxicity [25]; patients who wear contact lenses or have concomitant ocular surface diseases, as well as patients who receive high doses of ocular drugs or prolonged local treatments, must exercise caution when using drugs containing preservatives.

Ophthalmic bilastine is a preservative-free formulation, and its activity in reducing ocular itching was shown here to be noninferior to that of ketotifen. Moreover, ophthalmic bilastine showed superior comfort and tolerability upon instillation. The new once-daily bilastine ophthalmic formulation improved the signs and symptoms of AC while avoiding the potential undesired effects induced by the preservatives contained in other antihistamine eyedrops [23,24].


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Interpretation of our results is subject to limitations. For example, the CAC model has no assessment for the late-phase response of the drug; this would have required a modification of the model. Quality-of-life outcomes, a relevant aspect for allergy patients treated with eye drops, were not evaluated. At the time the clinical development plan was drawn up and this study was conducted (first visit, first patient on April 7, 2018 and last visit, last patient on August 10, 2018), there were no multidose ophthalmic formulations of preservative-free ketotifen available. Therefore, we selected the preserved ketotifen multidose formulation to homogenize the administration device (all the products in multidose containers) and thus maintain a double-blind study. Finally, the drug was instilled twice, and no evaluation was made of repeated, daily use of bilastine 0.6%. This topic has been further evaluated in an 8-week safety study (publication in process).

In conclusion, the new bilastine 0.6% preservative-free once-daily ophthalmic formulation proved to be noninferior to ketotifen 0.025% in reducing ocular itching at the onset of action and to maintain its efficacy up to 16 hours after treatment, thus supporting once-daily dosing. No safety and tolerability concerns were observed, and ocular comfort upon instillation was shown to be better than with the ketotifen eye drops tested.

## Acknowledgments

The authors would like to acknowledge Francisco López de Saro (Trialance SCCL) for medical writing assistance during the preparation of this manuscript.

### *Funding*

This work was funded by FAES Farma SA (Spain) and partially supported by the Government of the Basque Country (Economic Development and Infrastructures Department) through the HAZITEK program (grant number: ZE-2019/00004, 2019).

### *Conflicts of Interest*

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

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*Manuscript received November 30, 2022; accepted for publication January 24, 2023.*

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