Bilastine 0.6% preservative-free eye drops, a once-daily treatment for allergic conjunctivitis

Short title: Bilastine 0.6% eye drops for allergic conjunctivitis

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Abstract

Background: Bilastine is a second-generation antihistamine approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. This trial evaluated the efficacy and safety of a new bilastine 0.6% preservative-free eye-drops formulation for the symptomatic treatment of allergic conjunctivitis.

Methods: This phase 3, multicenter, double-masked, randomized study evaluated the efficacy, safety and tolerability of bilastine 0.6% ophthalmic solution compared to ketotifen 0.025% and vehicle. The primary efficacy endpoint was ocular itching reduction. The Ora-CAC® Allergen Challenge Model was used to assess ocular and nasal symptoms at 15 minutes (onset of action) and 16 hours post-treatment.

Results: Subjects (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 post-treatment (*P* <0.001). Ketotifen showed improvement compared to vehicle 15 minutes post-treatment (P <0.001). Bilastine demonstrated statistical non-inferiority to ketotifen for all 3 post-CAC timepoints at 15 minutes post-instillation, based on an inferiority margin of 0.4. Bilastine demonstrated improvement over vehicle (*P* <0.05) for conjunctival redness, ciliary redness, episcleral redness, chemosis, eyelid swelling, tearing, rhinorrhea, ear and palate pruritus and nasal congestion at 15 minutes post-treatment. Ophthalmic bilastine was safe and well tolerated. Mean drop comfort scores were significantly better (*P* <0.05) for bilastine compared with ketotifen immediately upon instillation, and similar compared with vehicle.

Conclusions: Ophthalmic bilastine effectively reduced ocular itching for 16 hours post-treatment, 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.

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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.

Introduction

Allergic conjunctivitis (AC) is an inflammatory process that can result from an IgE-mediated hypersensitivity reaction by direct contact of an allergen with the eye's conjunctival surface. This condition affects about 40% of the population and its incidence, as in the case for other allergic conditions, appears to be increasing [1]. AC generally affects both eyes, and patients report symptoms such as conjunctival pruritus (most bothering 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) can be observed, as well as moderate conjunctival and eyelid edema (swollen eyes). These symptoms can significantly impact the quality of life (QoL) of the patients [2,3]. AC treatment includes ophthalmic antihistamines, mast cell stabilizers, dual action agents, and corticosteroids. Most available multidose ophthalmic treatment contains preservative compounds that contribute to ocular surface toxicity [4,5]. Moreover, studies show that adherence decreases when several daily instillations are required, so single dose are 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 non-sedating H_1 antihistamine approved for oral symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children [6]. The efficacy of oral bilastine to reduce ocular symptoms in patients with allergic rhinoconjunctivitis has been extensively demonstrated in clinical trials [7–11]. Its safety and tolerability has also been characterized in children from 2 to 11 years, adolescents, adults, and elderly patients, revealing a good safety profile [12–15].

Pre-clinical *in vivo* biodistribution and pharmacokinetic studies in humans have shown that the ophthalmic formulation of bilastine is most concentrated in the

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conjunctiva, the intended target tissue, while drug absorption into the blood stream is minimal [16,17]. A recent dose finding study in adults showed that the ophthalmic bilastine 0.6% formulation rapidly reduces ocular itching and that this effect is maintained for 16 hours post-treatment, making it suitable for once-daily administration [18]. Bilastine 0.6% ophthalmic solution was also efficient compared to vehicle for controlling tearing, eyelid swelling, and nasal symptoms [18].

The primary objective of the present Phase 3 study was to evaluate the efficacy of the ophthalmic bilastine 0.6% formulation compared to its vehicle and to an ophthalmic multidose ketotifen 0.025% formulation (Zaditen®, Thea Laboratories) [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, which is a well-established and standardized methodology to evaluate 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 the external and internal factors are minimized. The Ora-CAC® Allergen Challenge Model (CAC hereinafter) of AC allows for a high degree of reproducibility and internal control and is the first clinical disease model accepted by the Food and Drug Administration (FDA) 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

This was a multi-center, double-masked, randomized, vehicle- and active-controlled, Phase 3, CAC study evaluating the efficacy and safety of ophthalmic bilastine 0.6% compared to ketotifen 0.025% and vehicle for the treatment of AC. The study was carried

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out at six ophthalmology clinics in the US between April 7th 2018 (first patient enrolled) and August 10th 2018 (last patient, last visit).

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

Study design

Efficacy of ophthalmic bilastine 0.6% and ketotifen 0.025% was evaluated using the Ora-CAC® Conjunctival Allergen Challenge Model (CAC) [20]. The methodology has been described in detail before, and a scheme of activities carried out in each visit is summarized in Figure 1 and Supplementary Figure 1. At the screening visit (Visit 1), patients signed the informed consent, demographic data and medical and medication history were acquired, and inclusion and exclusion criteria were reviewed. In Visit 2 a titration CAC was bilaterally performed with a perennial or seasonal allergen administered via micropipette. Subjects received one drop of a solubilized allergen in each eye, at the weakest dilution to which they were sensitized. If the subject 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 subject was sensitized were used, starting at the lowest dose. At all subsequent visits, subjects received the same type of allergen and same concentration identified at Visit 2. Subjects with a positive bilateral CAC reaction were considered qualifying subjects. 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.

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In Visit 3 a confirmation CAC was conducted, with each qualified subject receiving bilaterally one drop of the allergen solution at the same final dose which elicited a positive reaction at Visit 2. Ocular and nasal allergic signs and symptoms were assessed post-CAC.

During Visit 4a, subjects were randomized in 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. Subjects were asked to rate the comfort of the administered treatment 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.

In Visit 4b, 16 (±1) hours post-treatment instillation, each subject received one 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 post-CAC, by the investigator and the subject, using the Ora Calibra® scales.

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

At Day 15 (±3) the investigator made a telephone call to all subjects to inquire as to whether there were any changes in their medical history or medications, any AEs, emergency room visits, or hospitalizations since their last study visit.

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

Patient population

Inclusion criteria for participants were: age ≥18 years; a history of AC and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach); a positive bilateral post-CAC reaction

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(defined as having scores of ≥2 ocular itching and ≥2 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 two out of the first three 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 providing informed consent.

Exclusion criteria were: contraindications or sensitivities to the use of bilastine, ketotifen, or the vehicle; having any ocular condition that, in the investigators opinion, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of 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 first CAC at Visit 2 and during the study period (systemic antihistamines, decongestants, monoamine oxidase inhibitors, all topical ophthalmic preparations, lid scrubs, prostaglandins, NSAIDs, 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 redness in any vessel bed); significant illness that the investigator felt could be expected to interfere with the subject's health or with the study parameters. Female volunteers who were pregnant, planning a pregnancy or lactating were also excluded while female of childbearing potential was required to have a negative pregnancy test 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 (Leioa, Spain), and ketotifen multidose ophthalmic solution 0.025% (Zaditen®) was acquired from Laboratories Théa (Clemont-Ferrand, France). Ketotifen ophthalmic solution Vehicle was provided by FAES Farma. All selected products were in multi-dose containers. At the time of the study,

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multidose ketotifen without preservatives was not available, therefore, multidose ketotifen with preservatives was selected.

Ocular itching, the primary efficacy outcome, was evaluated by the subject at 3 (±1), 5 (±1), and 7 (±1) minutes post-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 measured by the subject were evaluated at 7 (±1), 15 (±1), and 20 (±1) minutes post-CAC at visits 4b and 5 (See Supplementary Methods). The safety variables monitored during the study were those routinely captured to monitor ocular health in an allergy clinical study. The incidence of subjects with any TEAEs (ocular and non-ocular TEAEs scored separately) during the study was the key safety variable (See Supplementary Methods).

Tolerability outcomes were: a drop comfort subject-assessment 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 more comfort); and a drop comfort subject-assessment at 3 minutes post-instillation using the Ora Calibra® Drop Comfort Questionnaire with subjects 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 subjects were to be randomized at Visit 4a in a 2:2:1 ratio across the three treatment arms (90 to bilastine 0.6%; 90 to ketotifen 0.025%; 45 subjects to vehicle). It was expected that approximately 5% of subjects would discontinue from the trial prior to completing Visit 5.

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

Ninety subjects in the bilastine treatment group and 90 subjects in the ketotifen treatment group produced a 96% power to reject the null hypotheses corresponding to the non-inferiority test for ocular itching (H_{20}) for a single time point. This calculation assumed a non-inferiority margin of Δ=0.40, a one-sided significance level of 0.025, an actual treatment difference of 0.10 in favor of bilastine, and a SD of 0.90 units. Furthermore, the same sample size and assumptions produced an 88.5% power to show that bilastine was non-inferior to ketotifen in terms of ocular itching scores for all 3 time points at Visit 5. In this study ketotifen was administered as 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 either to bilastine nor vehicle were made at visit 4b (16h).

Ninety subjects in the ketotifen treatment group and 45 subjects in the vehicle treatment group produced a >99.9% power to reject H_{30} (no difference in ocular itching between ketotifen and vehicle treated subjects) for a single time point. This calculation assumed a two-sided significance level of 0.05, a treatment difference of 1.1 units, and a 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

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Visit 5 for ocular itching between ketotifen and vehicle-treated subjects, assuming independence among 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 (MCMC), Last Observation Carried Forward (LOCF), and Multiple Imputations using 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. All statistical tests were two-sided with a significance level of 0.05 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 standard deviation. Summaries for discrete variables included frequency counts and percentages.

Results

A total of 228 subjects were randomized to the three study groups (Supplementary Figure 1), and 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 subjects in each eye at 15 minutes and 16 hours post-instillation of study medication, at 3, 5, and 7 minutes after CAC. The bilastine-treated group demonstrated statistically significant ($p < 0.001$) efficacy in reducing ocular itching compared to the vehicle group at all time points at both 15 minutes and 16 hours

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post-treatment (Fig. 2). The ketotifen group showed statistically significant improvements compared to vehicle at all three post-CAC time points 15 minutes post-treatment. Comparison of the bilastine and ketotifen groups demonstrated that bilastine was statistically non-inferior at all three post-CAC time points 15 minutes post-instillation of study medication, based on an inferiority margin of 0.4.

Secondary efficacy endpoints

For conjunctival redness, a secondary efficacy endpoint, treatment differences were statistically significant ($p < 0.05$) for bilastine 0.6% compared to vehicle at all time points at 15 minutes post-instillation (Figure 3A). However, no statistically significant treatment differences were observed for bilastine compared to vehicle 16 hours post-treatment ($p=0.0663$, $p=0.5933$, and $p=0.5850$ for the 7-, 15- and 20-minute timepoints, respectively). The non-inferiority test between bilastine and ketotifen demonstrated significant p-values at all 3 timepoints in visit 5 (onset of action), indicating that bilastine was non-inferior to ketotifen based in a non-inferiority margin of 0.4 ($p<0.0001$ for all time points).

Also, mean treatment differences for bilastine were statistically significant ($p < 0.05$) compared to vehicle at most post-CAC time points 15 minutes post-treatment for other secondary efficacy endpoints: ciliary redness ($p < 0.0001$), episcleral redness ($p < 0.0001$), chemosis ($p=0.0014$), eyelid swelling ($p=0.0008$), tearing ($p=0.0074$), rhinorrhea ($p=0.0007$), nasal pruritus ($p=0.0219$), ear or palate pruritus ($p=0.0066$) and nasal congestion ($p=0.0011$) (Figure 3).

Bilastine demonstrated significant p values for the non-inferiority 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 bilastine is non-inferior to ketotifen based on a non-inferiority margin of 0.4 (Figure 3).

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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 of them were ocular adverse events, three reported by subjects 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 causality assessment, none were considered related to study medication. There were no other general concerns raised by any of the ophthalmic examinations.

Tolerability

The mean drop comfort scores self-reported immediately upon instillation by subjects in the bilastine group were significantly lower ($p<0.05$) than the mean in the ketotifen group (lower score indicating more comfort). Mean drop comfort scores in the bilastine group were: 0.76 immediately after study medication instillation, 0.79 one minute after instillation, and 0.78 at the 2 minutes post-instillation. In the ketotifen group mean drop comfort scores were 1.52, 1.08, and 0.95 at immediately, 1 minute, and 2 minutes post-instillation respectively.

A statistically significant difference was reported in drop comfort immediately upon instillation between the bilastine treatment group and the ketotifen group ($p=0.0003$), which showed that bilastine was significantly more comfortable than ketotifen. However, no statistically significant differences were reported by subjects in drop comfort between the bilastine treatment group, or the ketotifen group, and the vehicle group at 1- and 2-minutes post-instillation (Fig. 4A).

Regarding the Ora Calibra® Drop Comfort Questionnaire, the assessment was performed 3 minutes after instillation and responses were similar between the three treatment groups. Generally, bilastine and ketotifen presented overall similar profiles, but

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more subjects selected the terms ‘smooth’ and ‘soothing’ for the bilastine formulation than for ketotifen. A burning sensation was selected by 3% of the subjects in the ketotifen group but by only 1% in the bilastine group.

Discussion

This randomized phase 3 clinical trial compared the efficacy, safety and tolerability of a newly developed ophthalmic formulation of bilastine for the relief of signs and symptoms of AC compared to that of ketotifen and vehicle. The results showed that bilastine 0.6% achieved the primary efficacy endpoint of reduction of ocular itching both at onset and duration of action (15 minutes and 16 hours, respectively, post-treatment instillation). Additionally, bilastine was non-inferior to ketotifen at onset of action. Regarding secondary efficacy endpoints, the differences of bilastine with 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 demonstrated non inferiority versus multidose ketotifen.

Moreover, the bilastine ophthalmic formulation was reported as 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 antihistamine topical formulation to alleviate 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 allergic conjunctivitis because of their ability to reduce symptoms and their tolerability [3,5]. Most topical treatments, even those with dual-acting agents, require repeated daily administration, contributing to lack of treatment adherence and consequently suboptimal control of AC symptoms [23,24]. Additionally, those

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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 bilastine could be used as a once-a-day treatment for AC. In this study, ophthalmic bilastine 0.6% formulation was compared with a ketotifen multidose ophthalmic solution 0.025% (Zaditen®), a dual-activity agent with antihistamine and mast-cell stabilizing activity. Zaditen multidose formulation contains benzalconium chloride 0.1 mg/mL, a surfactant preservative which has been shown to induce ocular surface toxicity [25]; patients who wear contact lenses or suffer from concomitant ocular surface diseases, as well as patients administered with high doses of ocular drugs or prolonged local treatments must be cautious when using drugs containing preservatives.

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

However, there are some limitations that must be considered in the interpretation of these results. For example, the CAC model has no assessment for the late-phase response of the drug, it would have required a modification of the model. No quality-of-life outcomes were evaluated, a relevant aspect for allergy patients treated with eye drops. 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, to homogenize the administration device (all the products in multidose containers), the preserved ketotifen multidose formulation was selected in

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order to maintain a double-blind study. Finally, the drug was instilled two times in the patients, and no evaluation was made of repeated, daily use of bilastine 0.6%. This topic has been evaluated in further eight-week safety study (publication in process). In conclusion, this new bilastine 0.6% preservative-free once daily ophthalmic formulation has shown to be non-inferior ito ketotifen 0.025% in reducing ocular itching at the onset of action, and to maintain its efficacy up to 16 hours post-treatment, supporting a once-daily dosing. No safety and tolerability concerns were observed, and ocular comfort upon instillation was shown to be better than with the tested ketotifen eye drops.

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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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Tables

Table 1. Patient baseline demographic characteristics (intent-to-treat population[a]).

Variable	Bilastine (N=91)	Ketotifen (N=90)	Vehicle (N=47)	All subjects (N=228)
Age (years)				
Mean (SD)	45.9 (12.9)	41.7 (12.1)	45.1 (16.0)	44.1 (13.4)
<65 years, N (%)	85 (93.4)	89 (98.9)	43 (91.5)	217 (95.2)
≥65 years, N (%)	6 (6.6)	1 (1.1)	4 (8.5)	11 (4.8)
Sex (male), N (%)				
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, N (%)				
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, N (%)				
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 ITT population comprised the 228 randomized subjects who received their first dose of bilastine at visit 4a.

SD, standard deviation

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Table 2. Adverse events (safety population, N=228)

	Bilastine (N=91)	Ketotifen (N=90)	Vehicle (N=47)	All subjects (N=228)
Number of TEAEs	4	2	1	7
Subjects with at least one TEAE, N (%)	4 (4.4)	1 (1.1)	1 (2.1)	6 (2.6)
Number of ocular TEAEs	3	2	0	5
Subjects with at least one ocular TEAE, N (%)	3 (3.3)	1 (1.1)	0	4 (1.8)
Severity of ocular TEAEs, N (%)				
Mild	3 (3.3)	1 (1.1)	0	4 (1.8)
Moderate	0	0	0	0
Severe	0	0	0	0
Eye disorders, N (%)				
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)
Non-ocular TEAEs, N (%)	1	0	1	2
Subjects with at least one non-ocular TEAE, N (%)	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)

Note: N in the headers represents the total number of subjects 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 which occurred after the first dose of study medication. All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1

TEAE, treatment-emergent adverse event

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Figure legends

Figure 1. Study design according to the Ora-CAC® Allergen Challenge Model.

Abbreviations: AEs, adverse events; CAC, conjunctival allergen challenge; h, hours; m, minutes.

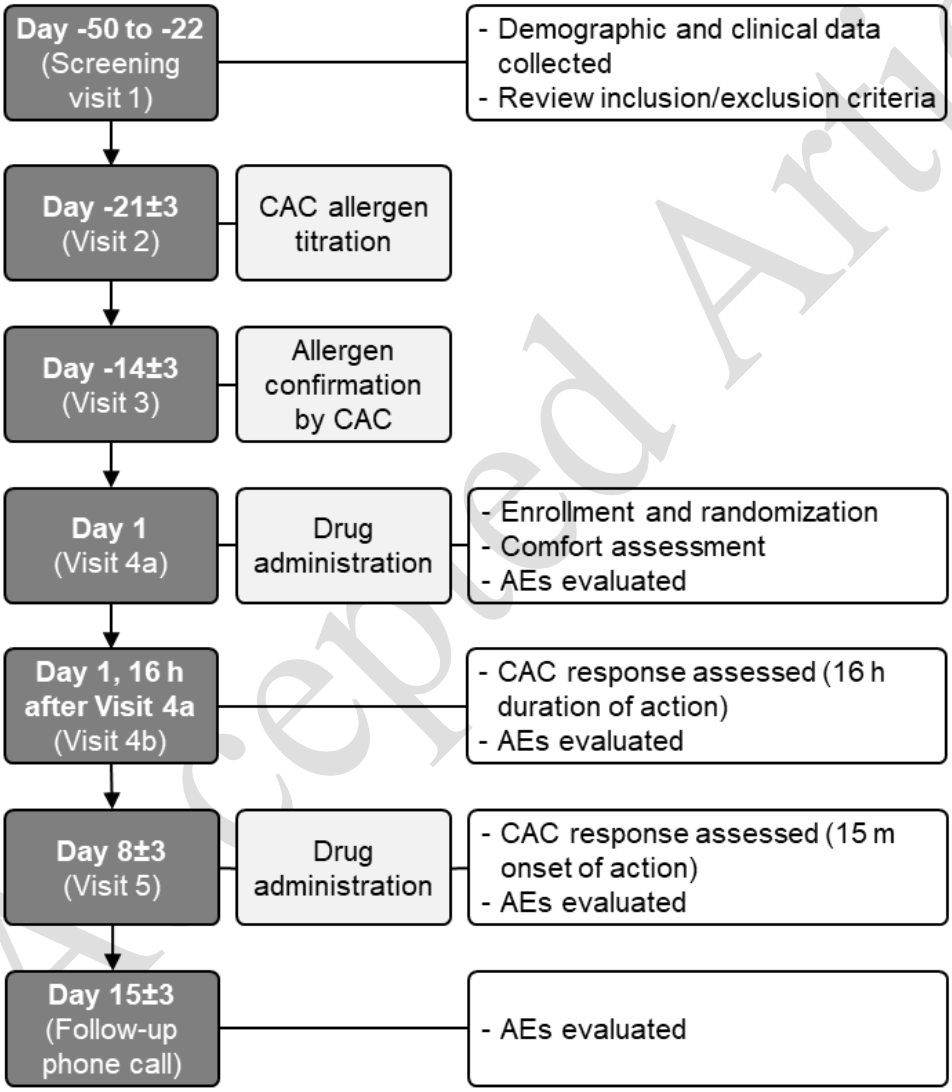

Figure 2. Evaluation of ocular itching 15 m post-treatment and 16 h post-treatment in patients treated with bilastine 0.6% (light grey bars) and ketotifen 0.025% (dark grey bars). Subjects were assessed in each eye using a 5-point scale (0-4, half units allowed) at Visit 5 (15 minutes post-instillation of study medication) and Visit 4b (16 hours post-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<0.05; **, p<0.001; ***, p<0.0001. Abbreviations: h, hours; m, minutes.

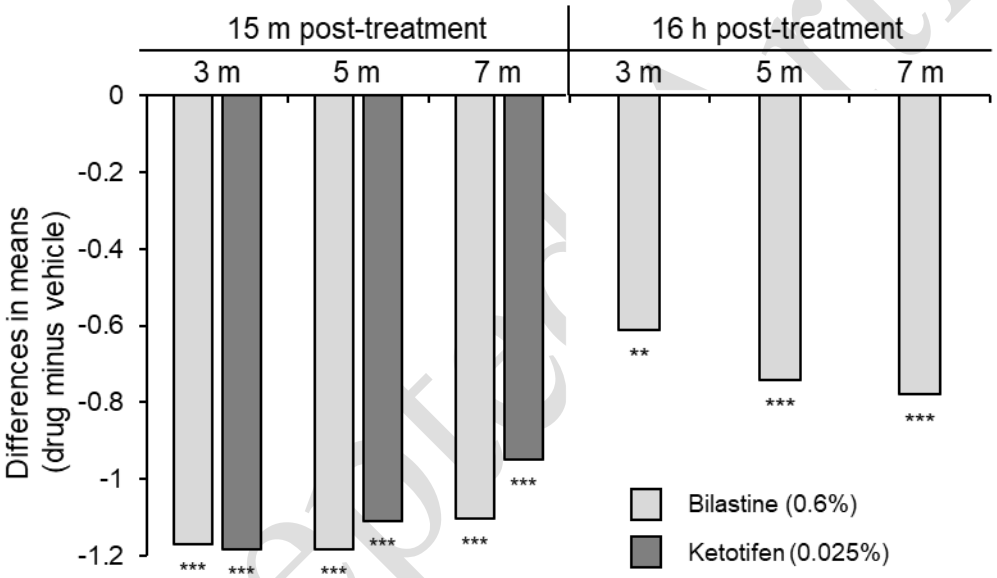

Figure 3. Evaluation of secondary endpoints in the study. Subjects were assessed in each eye using a 5-point scale (0-4, half units allowed) at Visit 5 (15 minutes post-instillation of study medication) and Visit 4b (16 hours post-instillation of study medication) at 7, 15, and 20 minutes after CAC. A, conjunctival redness; B, ciliary redness; C, episcleral redness; D, chemosis; D, eyelid swelling; E, tearing; F, rhinorrhea; G, nasal pruritus; H, ear or palate pruritus; and I, nasal congestion. In all cases data on bilastine 0.6% is shown by light grey bars and data on ketotifen 0.025% in dark grey bars. Statistical significance is indicated as follows: *, $p<0.05$; **, $p<0.001$; ***, $p<0.0001$. Abbreviations: h, hours; NC, no change; m, minutes.

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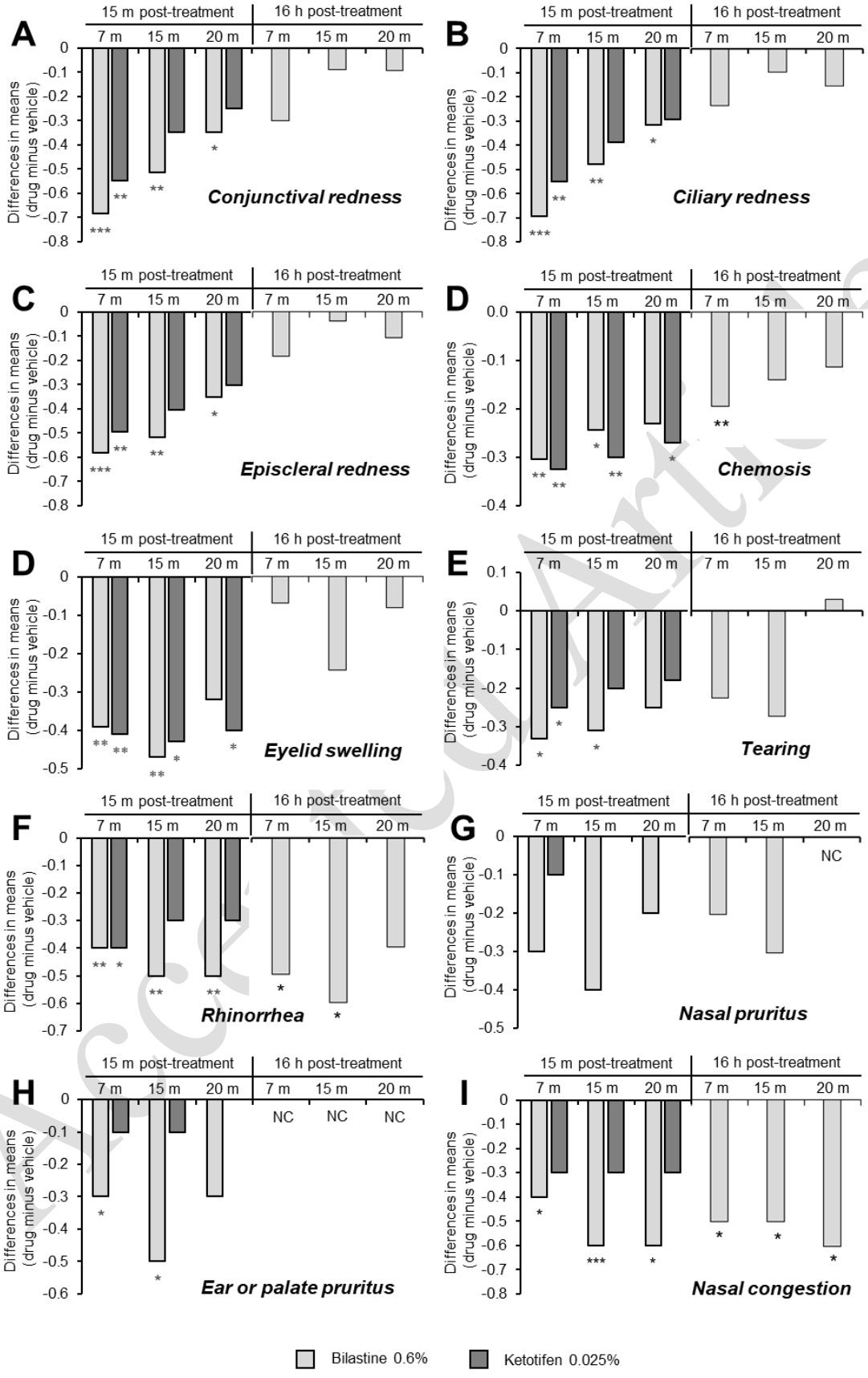

Figure 4. Mean scores of the Drop Comfort Scale (0-10). No significant differences were observed between scores for bilastine 0.6% or ketotifen 0.025% and vehicle at any of the timepoints.