Efficacy of once-daily ophthalmic bilastine for the treatment of allergic conjunctivitis: a dose-finding study

Short title: Bilastine for allergic conjunctivitis

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Abstract

Background and objectives: Bilastine is a non-sedating second-generation antihistamine for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. This trial 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: This phase 2, single-center, double-masked, randomized study evaluated the efficacy of 3 doses of a bilastine ophthalmic formulation (0.2%, 0.4%, and 0.6%) compared to vehicle for the treatment of allergic conjunctivitis. The primary efficacy endpoint was ocular itching reduction. The Ora-CAC® Conjunctival Allergen Challenge model was used to assess ocular and nasal symptoms at the onset of action (15 minutes), 8- and 16-hours post-treatment. Tolerance and safety were also evaluated.

Results: A total of 121 adults with seasonal and/or perennial ocular allergy were randomized. Bilastine ophthalmic formulation 0.2%, 0.4% and 0.6% were significantly superior ($p>0.001$) to vehicle for the treatment of ocular itching at 3, 5 and 7 minutes post-challenge at onset of action (15 minutes) and 8 hours post-treatment. Bilastine 0.6% was also effective at 16 hours post-treatment. Treatment differences for bilastine 0.6% were statistically significant ($p<0.001$) 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 in rapidly reducing ocular itching. The 0.6% formulation was effective up to 16 hours post-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.

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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.

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Palabras clave: Conjuntivitis alérgica. Antihistamínico. Prurito ocular. Bilastina; una vez al día. Sin preservativos.

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Introduction

Allergic conjunctivitis (AC) is a highly prevalent hypersensitivity disorder of the ocular conjunctiva affecting up to 40% of the adult population [1]. It is frequently concomitant with allergic rhinitis, but some patients (6-30%) can develop ocular symptoms without nasal involvement [2,3]. The symptoms of allergic conjunctivitis include ocular itching, conjunctival redness, and tearing, and may cause a significant impact on quality of life [4,5]. Current treatments aim to control and relief symptoms and include systemic or topical antihistamines, mast cell stabilizers, dual action agents, anti-inflammatories, 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, and is currently approved to treat children aged 6–11 years who weigh ≥20 kg, while some other regulatory agencies deemed approval for children older than 2 years [10,11].

The preclinical pharmacology of bilastine revealed that toxicity occurred only at levels significantly higher than the proposed topical ocular dosing [12,13]. Oral bilastine has shown to significantly reduce 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 ten Phase 2 and 3 studies conducted in patients, one including with a one 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, post-

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authorization 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 in 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 side effects [10]. However, adherence decreases if several daily instillations are required, as shown by treatment compliance studies in other ocular conditions [30]. To minimize 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, bilastine ophthalmic formulation has been developed for the specific treatment of allergic conjunctivitis. Pre-clinical *in vivo* biodistribution and pharmacokinetic studies in humans with this formulation showed that bilastine is predominantly distributed in the conjunctiva, the intended target tissue, while it is poorly absorbed in the blood stream [31,32].

To assess the efficacy and safety of ophthalmic bilastine we designed a study methodologically based in the Ora-CAC® Conjunctival allergen-challenge model (CAC), 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, after topical application of an allergen, on the external ocular surface, and evaluate the effect of several 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 FDA, the EMA, and the Japanese Pharmaceuticals and Medical Devices Agency. Here we describe the results of this dose-finding, vehicle-controlled, randomized clinical study evaluating the efficacy, safety and tolerance of three doses of bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) for the symptomatic treatment of AC.

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Methods

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

The study evaluated the efficacy of three doses of bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) compared to vehicle (formulation without bilastine), for the treatment of AC, as well as safety and tolerability. Efficacy was evaluated using the Ora-CAC® conjunctival allergen challenge model (Ora Inc, MA, USA) [33]. In this model 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, efficacy of the study drug is tested in combination with the CAC model to evaluate and measure the signs and symptoms of AC. The time points to evaluate efficacy for 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 informed consent. The study protocol, informed consent form and assent form, Health Information Portability and Accountability (HIPAA) 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 a scheme of the study design. After a screening visit to review inclusion and exclusion criteria (see below), patients underwent a bilateral CAC to titrate an

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allergen and evaluate the subject's individual allergic sensitivity (visit 2). One drop per eye of a solubilized allergen to which the subject was sensitized was administered at the weakest dilution into the conjunctival sac.

If the subject failed to react within 10 (±2) minutes, increasingly concentrated doses were instilled at approximately ten-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 subject was sensitized were used, starting at the lowest dose. At all subsequent visits, subjects received the same type of allergen and concentration identified at visit 2. Upon completion of the initial CAC titration, subjects received an ocular examination by the investigator to evaluate all efficacy measures and confirm the subject's qualification. Subjects were also asked to self-assess their ocular and nasal allergic symptoms using the Ora-CAC® scales. Any subject who failed to test positively was excluded from the study.

On visit 3 subjects were evaluated for visual acuity using an ETDRS chart and slit lamp biomicroscopy was conducted. Ocular and nasal allergic signs and symptoms were assessed pre-CAC by the investigator and subject using the Ora Calibra® clinical grading scales. These evaluations were carried out at all subsequent visits. On visit 3, a confirmation CAC was also conducted.

On visit 4 duration of action after 16 hours of drug instillation was assessed. Visit 4 was separate in 2 phases, visits 4a and 4b. On visit 4a, subjects who qualified to continue in the study were randomized to one of the four 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), subjects 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.

In visit 4b, 16 (±1) hours after study drug instillation (visit 4a), each subject received bilaterally one drop of the allergen solution of the type and dose that elicited a

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positive reaction at visit 2. Ocular and nasal allergic signs and symptoms were assessed post-CAC by the investigator and the subject at the predetermined timepoints using Ora Calibra® grading scales. Once subjects received the first study drug, AEs were considered to be TEAEs (Treatment-emergent adverse events) and assessed post-CAC from visit 4b onwards.

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

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

Study population

Inclusion criteria for participants were: asymptomatic patients aged ≥18 years with 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 (defined as having scores of ≥2 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 two out of the first three time points 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.

Exclusion criteria were: contraindications or sensitivities to the use of bilastine 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

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to Visit 2 and during the study (systemic antihistamines, decongestants, monoamine oxidase inhibitors, all topical ophthalmic preparations, lid scrubs, prostaglandins, NSAIDs, 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 redness in any vessel bed); significant illness the investigator felt could be expected to interfere with the subject's health or with the study parameters; or pregnancy.

Efficacy endpoints and assessments

The primary efficacy endpoint was ocular itching evaluated by the subject at: 3 (±1), 5 (±1), and 7 (±1) minutes post-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), using a 0 to 4 Ora Calibra scale: 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 of a 5-point scale for all 3 post-CAC time points (3(±1), 5(±1), and 7(±1) minutes post-CAC) at one of three study visits, and at least 1 unit for the majority (2:3) of these post-CAC time points, 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 post-CAC at visits 4b, 5b, and 6, on a 0-4 scale, with 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 subject.

Similarly, an exploratory efficacy endpoint was measured: ocular itching and redness summarized by allergen type (seasonal and perennial).

Safety and tolerability endpoints

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The safety endpoints were: adverse events (AE) in all office visits; visual acuity using ETDRS chart at visits 2, 3, 4a, 4b, 5a, 5b, and 6 pre-CAC, and also post-CAC at visit 6; slit lamp biomicroscopy at visits 2, 3, 4a, 4b, 5a, 5b, and 6 pre-CAC, and also post-CAC at visit 6 for examination of the anterior chamber, conjunctiva, cornea, eyelid, and lens; intraocular pressure at visits 2 and 6 post-CAC; and dilated fundoscopy at visits 2 and 6 post-CAC. Once the assigned bilastine or vehicle solutions were instilled, all adverse events communicated throughout the rest of the study were considered treatment-emergent adverse events (TEAEs).

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

Sample size determination

Assuming a standard deviation of 0.95 units in each treatment arm and a study-wide two-sided type I error of 0.05 (a family-wise two-sided type I error of 0.0167), a sample size of 28 subjects 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 subjects at visit 6. Using these same assumptions, this sample size would have 87% power to show a statistical difference at visits 4b and/or 5b, at 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 subjects would discontinue from the trial prior to completing visit 6.

Statistical analysis

The primary efficacy analyses were conducted on the intention to treat (ITT) population with last observation carried forward (LOCF) for missing data using analysis of

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covariance (ANCOVA) 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 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.

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 time points, testing of ocular itching would continue for visits 5b (8 hours after administration) and 4b (16 hours after administration). If the comparison of ocular itching at visit 6 and at least one of visits 5b and 4b were statistically significant, then conjunctival redness would be tested according to a similar rational and following the same hierarchy, but with a reduced alpha level. Bonferroni's 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 standard deviation. Summaries for discrete variables included frequency counts and percentages.

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Results

A total of 121 subjects, 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 ocular itching reduction. All three concentrations of bilastine (0.2%, 0.4%, and 0.6%) showed statistically significant differences in reducing ocular itching ($p<0.001$) 15 minutes and 8 and 16 hours post-treatment instillation compared to vehicle (Figure 3). Mean treatment differences at all post CAC time points were ≥1 unit for bilastine 0.6%. Treatment differences for bilastine 0.2% and 0.4% were ≥1 unit at all post CAC time points at 15 minutes and 8 hours post-treatment and ≥0.5 units at all time points at 16 hours post-treatment.

For conjunctival redness, only bilastine 0.6% had statistically significant differences as compared to vehicle in most timepoints in all visits (15 minutes, 8 and 16 hours post-treatment), while the 0.4% and 0.2% concentrations did not achieve significance in all the visits (Figure 4A).

Treatment differences for bilastine 0.6% were statistically significant ($p<0.001$) compared to vehicle at all post CAC time points 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 ($p<0.001$) for ocular itching regardless of allergen type at 15 minutes, and 8 and 16 hours post-treatment (Figure 5).

Safety

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Nineteen TEAEs were reported by 18 (14.9%) subjects (Table 2). A similar number of TEAEs were reported in the bilastine 0.2% group and the vehicle group, with fewer reported in the bilastine 0.4% and no ocular TEAEs reported in the bilastine 0.6% group. Most TEAEs (14/19) were mild in severity, no subjects experienced serious adverse events, and none of the moderate TEAEs (ocular and non-ocular) reported by all treatment groups were considered related or likely to be related to treatment.

There were no other general concerns raised by any of the ophthalmic examinations. No study discontinuations due to a related TEAE were observed, and only one was considered related to the study drug: a mild headache reported by a subject in the bilastine 0.4% group.

Comfort

Subjects reported that all the bilastine ophthalmic solutions were of similar comfort to the vehicle ophthalmic solution; all comfort scale scores were low, ranging between 0.60 to 1.08 on the 10-point scale (lower scores indicate more comfort) among all four treatment groups (Figure 6A). Subjects also more frequently identified the bilastine solution as more “soothing” than the vehicle solution (Figure 6B).

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Discussion

This randomized phase 2 clinical trial is the first to assess the efficacy and safety of three doses of an ophthalmic, preservative-free, formulation of bilastine (0.2%, 0.4%, and 0.6%), compared with its vehicle, for the symptomatic treatment of AC. We found that all three 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. Bilastine 0.6% also presented statistically significant difference compared to vehicle at all post-CAC time points 16 hours after treatment for tearing and eyelid swelling, and for nasal symptoms. The results also showed that bilastine 0.6% was well tolerated in the range of times tested, and patients reported comfort comparable with vehicle.

Ocular itching is the most bothersome symptom reported by patients with AC, and greatly affects their quality of life [43]. Oral antihistamines, although effective, often have a later local onset of action and the potential for systemic side-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, a 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 post-treatment visit. For conjunctival redness, statistically significant differences with respect to vehicle could be observed for 7 minutes post-CAC timepoints 16 hours after treatment although the pathophysiology of conjunctival redness is not directly targeted by antihistamines [44].

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An analysis of allergen type, seasonal or perennial, found significant differences between bilastine 0.6% and vehicle ($p<0.001$) for ocular itching regardless of allergen type at 15 minutes, and 8 and 16 hours post-treatment (Figure 5), with differences at all post-CAC time points ≥1 unit in favor of bilastine 0.6%. Oral bilastine had previously 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 allergic conjunctivitis.

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, subjects reported that the bilastine ophthalmic solutions were of similar comfort to 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], but there is a need for comparative studies to investigate their relative efficacy [51]. In this regard, a phase 3 clinical trial comparing bilastine 0.6%, ketotifen 0.025%, and vehicle was recently completed, and results 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 a good tolerability. The bilastine preservative-free formulation demonstrated to be highly comfortable as assessed by patients. 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, MA, USA). GH, PA, and NF are employees of FAES FARMA (Bizkaia, Spain). JBC is a consultant to Ora Inc.

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References

1. Dupuis P, Prokopich CL, Hynes A, Kim H. A contemporary look at allergic conjunctivitis. Allergy Asthma Clin Immunol. 2020;16:5.

2. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol. 2010;126:778-783.e6.

3. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. Curr Opin Allergy Clin Immunol. 2015;15:482–8.

4. Sánchez-Hernández MC, Montero J, Rondon C, Benitez del Castillo JM, Velázquez E, Herreras JM, et al. Consensus document on allergic conjunctivitis (DECA). J Investig Allergol Clin Immunol. 2015;25:94–106.

5. Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: Diagnosis and Management of Allergic Conjunctivitis. Ann Allergy Asthma Immunol. 2020;124:118–34.

6. Leonardi A, Silva D, Perez Formigo D, Bozkurt B, Sharma V, Allegri P, et al. Management of ocular allergy. Allergy. 2019;74:1611–30.

7. Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. Cochrane Database Syst Rev. 2015;CD009566.

8. Bartra J, Mullol J, Montoro J, Jauregui I, del Cuvillos A, Davila I, et al. Effect of bilastine upon the ocular symptoms of allergic rhinoconjunctivitis. J Investig Allergol Clin Immunol. 2011;21 Suppl 3:24–33.

9. Scaglione F. Safety profile of bilastine: 2nd generation H1-antihistamines. Eur Rev Med Pharmacol Sci. 2012;16:1999–2005.

10. Church MK, Tiongco-Recto M, Ridolo E, Novak Z. Bilastine: a lifetime companion for the treatment of allergies. Curr Med Res Opin. 2020;36:445–54.

11. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of product characteristics Ilaxten 10 mg orodispersible tablets, bilastine 2018; Available from: https://mhraproductsproduction.blob.core.windows.net/docs/2f799931ac3572bd33b801e5b15e6168c95b156a. (Accessed 22 June 2020).

12. Lucero ML, Gonzalo A, Mumford R, Betanzos M, Alejandro A. An overview of bilastine metabolism during preclinical investigations. Drug Chem Toxicol. 2012;35 Suppl 1:18–24.

13. Lucero ML, Gonzalo A, Ganza A, Leal N, Soengas I, Ioja E, et al. Interactions of bilastine, a new oral H(1) antihistamine, with human transporter systems. Drug Chem Toxicol. 2012;35 Suppl 1:8–17.

14. Bachert C, Kuna P, Sanquer F, Ivan P, Dimitrov V, Gorina MM, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. Allergy. 2009;64:158–65.

doi: 10.18176/jiaci.0800

15. Kuna P, Bachert C, Nowacki Z, van Cauwenberge P, Agache I, Fouquert L, et al. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. Clin Exp Allergy. 2009;39:1338–47.

16. Okubo K, Gotoh M, Asako M, Nomura Y, Togawa M, Saito A, et al. Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study. Allergol Int. 2017;66:97–105.

17. Sastre J, Mullol J, Valero A, Valiente R. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo in the treatment of perennial allergic rhinitis. Curr Med Res Opin. 2012;28:121–30.

18. Jauregizar N, de la Fuente L, Lucero ML, Sologuren A, Leal N, Rodriguez M. Pharmacokinetic-pharmacodynamic modelling of the antihistaminic (H1) effect of bilastine. Clin Pharmacokinet. 2009;48:543–54.

19. Sadaba B, Gomez-Guiu A, Azanza JR, Ortega I, Valiente R. Oral availability of bilastine. Clin Drug Investig. 2013;33:375–81.

20. Zuberbier T, Oanta A, Bogacka E, Medina I, Wesel F, Uhl P, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. Allergy. 2010;65:516–28.

21. Church MK. Safety and efficacy of bilastine: a new H(1)-antihistamine for the treatment of allergic rhinoconjunctivitis and urticaria. Expert Opin Drug Saf. 2011;10:779–93.

22. Togawa M, Yamaya H, Rodriguez M, Nagashima H. Pharmacokinetics, Pharmacodynamics and Population Pharmacokinetic/Pharmacodynamic Modelling of Bilastine, a Second-Generation Antihistamine, in Healthy Japanese Subjects. Clin Drug Investig. 2016;36:1011–21.

23. Novák Z, Yáñez A, Kiss I, Kuna P, Tortajada-Girbés M, Valiente R, et al. Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases. Pediatr Allergy Immunol [Internet]. 2016 [cited 2020 Nov 20];27:493–8. Available from: https://onlinelibrary.wiley.com/doi/10.1111/pai.12555

24. Sologuren A, Vinas R, Cordon E, Riesgo SE, Del Mar Fores M, Senan MR, et al. Open-label safety assessment of bilastine in elderly patients with allergic rhinoconjunctivitis and/or urticaria. Allergy Asthma Proc. 2018;39:299–304.

25. Papadopoulos NG, Zuberbier T. The safety and tolerability profile of bilastine for chronic urticaria in children. Clin Transl Allergy. 2019;9:55.

26. Vozmediano V, Lukas JC, Encinas E, Schmidt S, Sologuren A, Valiente R, et al. Model-informed pediatric development applied to bilastine: Analysis of the clinical PK data and confirmation of the dose selected for the target population. Eur J Pharm Sci. 2019;128:180–92.

27. Rodríguez M, Vozmediano V, García-Bea A, Novak Z, Yáñez A, Campo C, et al. Pharmacokinetics and safety of bilastine in children aged 6 to 11 years with allergic rhinoconjunctivitis or chronic urticaria. Eur J Pediatr. 2020;179:801–5.

doi: 10.18176/jiaci.0800

28. Jauregui I, Bartra J, del Cuvillo A, Davila I, Ferrer M, Montoro J, et al. Bilastine and quality of life. J Investig Allergol Clin Immunol. 2011;21 Suppl 3:16–23.

29. Bousquet J, Ansotegui I, Canonica GW, Zuberbier T, Baena-Cagnani CE, Bachert C, et al. Establishing the place in therapy of bilastine in the treatment of allergic rhinitis according to ARIA: evidence review. Curr Med Res Opin. 2012;28:131–9.

30. Erdogan H, Cam O. The Effect Of Topical Antihistamines Used Single Dose Daily in Allergic Conjunctivitis. TOOPHTJ [Internet]. 2018 [cited 2021 May 22];12:330–7. Available from: https://openophthalmologyjournal.com/VOLUME/12/PAGE/330/

31. Torrens I, Ganza A, Hernández G, Gonzalo A, Zazpe A. [Preferential biodistribution of bilastine in conjunctiva after single drop administration of 0.6% ophthalmic solution in rabbits]. 2021;

32. Ochoa D, Román M, Belmonte C, Martín-Vilchez S, Mejía-Abril G, Abad-Santos F, et al. Pharmacokinetics and safety of a bilastine once-daily, preservative-free, ophthalmic formulation. Adv Ther. 2021;38:4070–81.

33. Abelson MB, Chambers WA, Smith LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. Arch Ophthalmol. 1990;108:84–8.

34. Abelson MB, Loeffler O. Conjunctival allergen challenge: models in the investigation of ocular allergy. Curr Allergy Asthma Rep. 2003;3:363–8.

35. Abelson MB, McLaughlin JT, Gomes PJ. Antihistamines in ocular allergy: are they all created equal? Curr Allergy Asthma Rep. 2011;11:205–11.

36. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, Calder V, Silva D, Kvenshagen BK, et al. Conjunctival allergen provocation test : guidelines for daily practice. Allergy. 2017;72:43–54.

37. Macejko TT, Bergmann MT, Williams JI, Gow JA, Gomes PJ, McNamara TR, et al. Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis. Am J Ophthalmol. 2010;150:122-127.e5.

38. Ciolino JB, McLaurin EB, Marsico NP, Ackerman SL, Williams JM, Villanueva L, et al. Effect of alcaftadine 0.25% on ocular itch associated with seasonal or perennial allergic conjunctivitis: a pooled analysis of two multicenter randomized clinical trials. Clin Ophthalmol. 2015;9:765–72.

39. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.

40. Gomes PJ, Ousler GW, Welch DL, Smith LM, Coderre J, Abelson MB. Exacerbation of signs and symptoms of allergic conjunctivitis by a controlled adverse environment challenge in subjects with a history of dry eye and ocular allergy. Clin Ophthalmol. 2013;7:157–65.

41. Ousler G, Devries DK, Karpecki PM, Ciolino JB. An evaluation of Retaine™ ophthalmic emulsion in the management of tear film stability and ocular surface staining in patients diagnosed with dry eye. Clin Ophthalmol. 2015;9:235–43.

42. Petrov A, Perekhvatova N, Skulachev M, Stein L, Ousler G. SkQ1 Ophthalmic Solution for Dry Eye Treatment: Results of a Phase 2 Safety and Efficacy Clinical

doi: 10.18176/jiaci.0800

Study in the Environment and During Challenge in the Controlled Adverse Environment Model. Adv Ther. 2016;33:96–115.

43. Virchow JC, Kay S, Demoly P, Mullol J, Canonica W, Higgins V. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients--an observational, cross sectional study in four countries in Europe. J Med Econ. 2011;14:305–14.

44. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol. 2005;115:118–22.

45. Mah FS, Rosenwasser LJ, Townsend WD, Greiner JV, Bensch G. Efficacy and comfort of olopatadine 0.2% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge. Curr Med Res Opin. 2007;23:1445–52.

46. Abelson MB, Torkildsen GL, Williams JI, Gow JA, Gomes PJ, McNamara TR. Time to onset and duration of action of the antihistamine bepotastine besilate ophthalmic solutions 1.0% and 1.5% in allergic conjunctivitis: a phase III, single-center, prospective, randomized, double-masked, placebo-controlled, conjunctival allergen challenge assessment in adults and children. Clin Ther. 2009;31:1908–21.

47. McLaurin EB, Marsico NP, Ackerman SL, Ciolino JB, Williams JM, Villanueva L, et al. Ocular itch relief with alcaftadine 0.25% versus olopatadine 0.2% in allergic conjunctivitis: pooled analysis of two multicenter randomized clinical trials. Adv Ther. 2014;31:1059–71.

48. Torkildsen G, Narvekar A, Bergmann M. Efficacy and safety of olopatadine hydrochloride 0.77% in patients with allergic conjunctivitis using a conjunctival allergen-challenge model. Clin Ophthalmol. 2015;9:1703–13.

49. Leonardi A, Capobianco D, Benedetti N, Capobianco A, Cavarzeran F, Scalora T, et al. Efficacy and Tolerability of Ketotifen in the Treatment Of Seasonal Allergic Conjunctivitis: Comparison between Ketotifen 0.025% and 0.05% Eye Drops. Ocul Immunol Inflamm. 2019;27:1352–6.

50. Malhotra RP, Meier E, Torkildsen G, Gomes PJ, Jasek MC. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. Clin Ophthalmol. 2019;13:403–13.

51. Kimchi N, Bielory L. The allergic eye: recommendations about pharmacotherapy and recent therapeutic agents. Curr Opin Allergy Clin Immunol. 2020;20:414–20.

doi: 10.18176/jiaci.0800

Tables

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

	Bilastine 0.2% (N=30)	Bilastine 0.4% (N=30)	Bilastine 0.6% (N=31)	Vehicle (N=30)	All subjects (N=121)
Age (years)					
Mean (SD)	50.4 (10.7)	47.0 (14.0)	51.8 (13.1)	48.3 (13.2)	49.4 (12.8)
<65 years, N (%)	28 (93.3)	27 (90.0)	27 (87.1)	27 (90.0)	109 (90.1)
≥65 years, N (%)	2 (6.7)	3 (10.0)	4 (12.9)	3 (10.0)	12 (9.9)
Sex (male), N (%)					
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, N (%)					
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 ITT population comprised the 121 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)

	Bilastine 0.2% (N=30)	Bilastine 0.4% (N=30)	Bilastine 0.6% (N=31)	Vehicle (N=30)	All subjects (N=121)
Number of TEAEs	8	3	1	7	19
Subjects with at least one TEAE, N (%)	8 (26.7)	3 (10.0)	1 (3.2)	6 (20.0)	18 (14.9)
Number of ocular TEAEs	5	1	0	2	8
Subjects with at least one ocular TEAE, N (%)	5 (16.7)	1 (3.3)	0	2 (6.7)	8 (6.6)
Severity of ocular TEAEs, N (%)					
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, N (%)	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, N (%)	1 (3.3)	0	0	0	1 (0.8)
Non-ocular TEAEs, N (%)	3	2	1	5	11
Subjects with at least one non-ocular TEAE, N (%)	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)

All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0
TEAE, treatment-emergent adverse event (adverse events reported after the subject received the study drug)

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Figure Legends

Figure 1. Study design according to the conjunctival allergen-challenge model.

AEs, adverse events; CAC, conjunctival allergen challenge

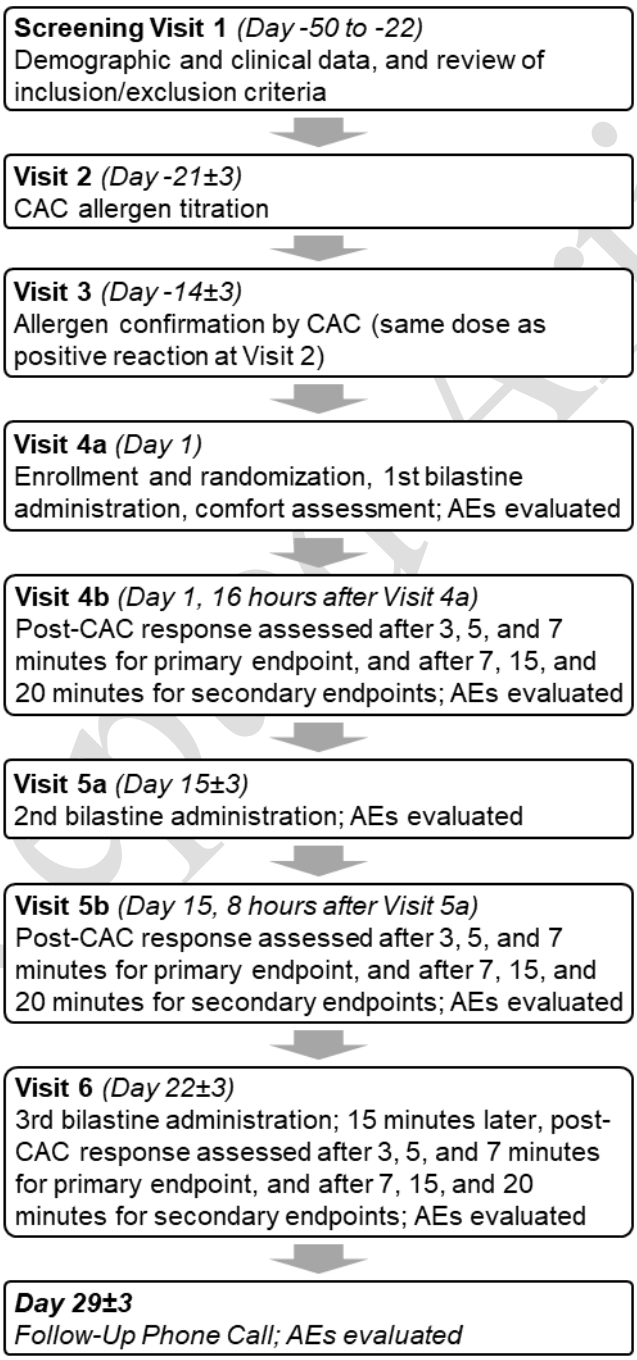

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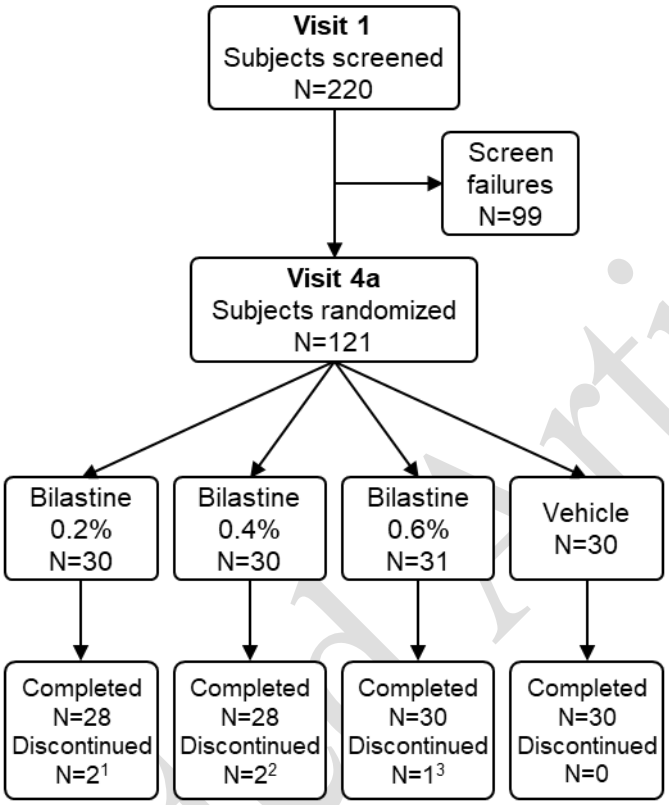
Figure 2. Study subjects' disposition.



[1] Patients were lost at follow-up.
[2] One patient presented clinically active signs of allergic conjunctivitis at visit 5a; a second patient was lost at follow-up.
[3] Discontinued because of investigator's decision at visit 5a (TEAE of hypoaesthesia).

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Figure 3. Evaluation of the primary endpoint, ocular itching, at visits 4b (16 hours post-treatment), 5b (8 hours), and 6 (15 minutes) by treatment group (treatment differences calculated as bilastine treatment minus vehicle). All differences were significant ($p<0.0001$), calculated using a two-sample t-test comparing the active treatment to vehicle.

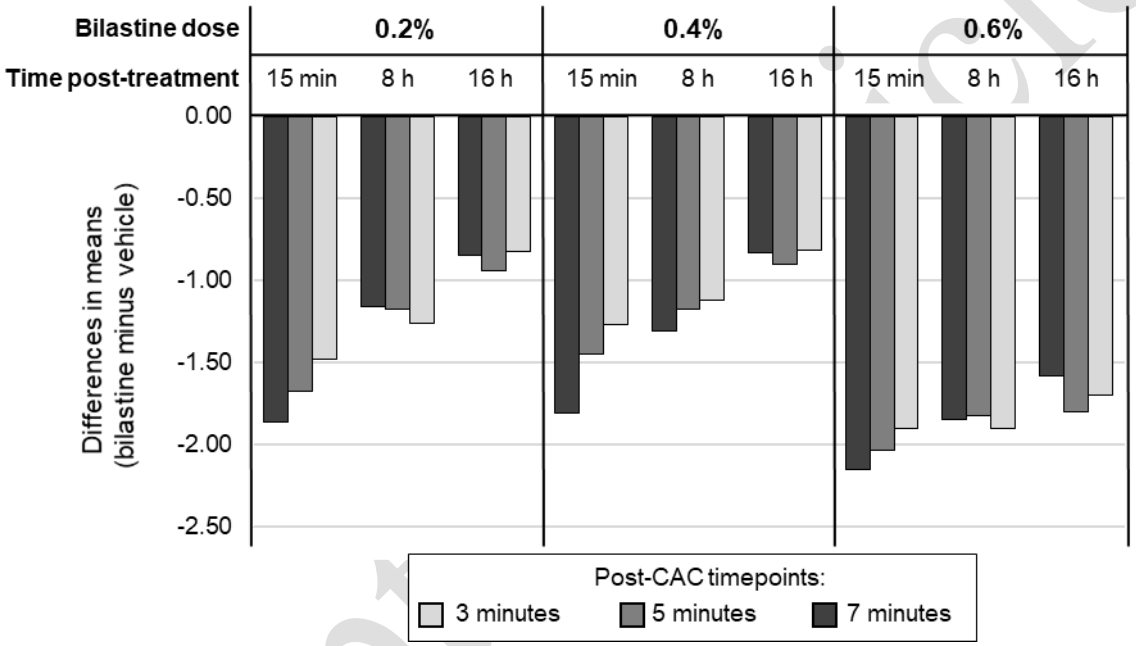

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Figure 4. Evaluation of the secondary endpoints at visits 4b (16 hours post-treatment), 5b (8 hours), and 6 (15 minutes) for the bilastine 0.6% group. **A,** ocular endpoints; **B,** nasal endpoints. Treatment differences calculated as bilastine 0.6% minus vehicle. Significance of differences indicated as follows: *, p<0.05; **, p<0.01; ***, p<0.001. Significance was calculated using a two-sample t-test comparing the active treatment to vehicle.

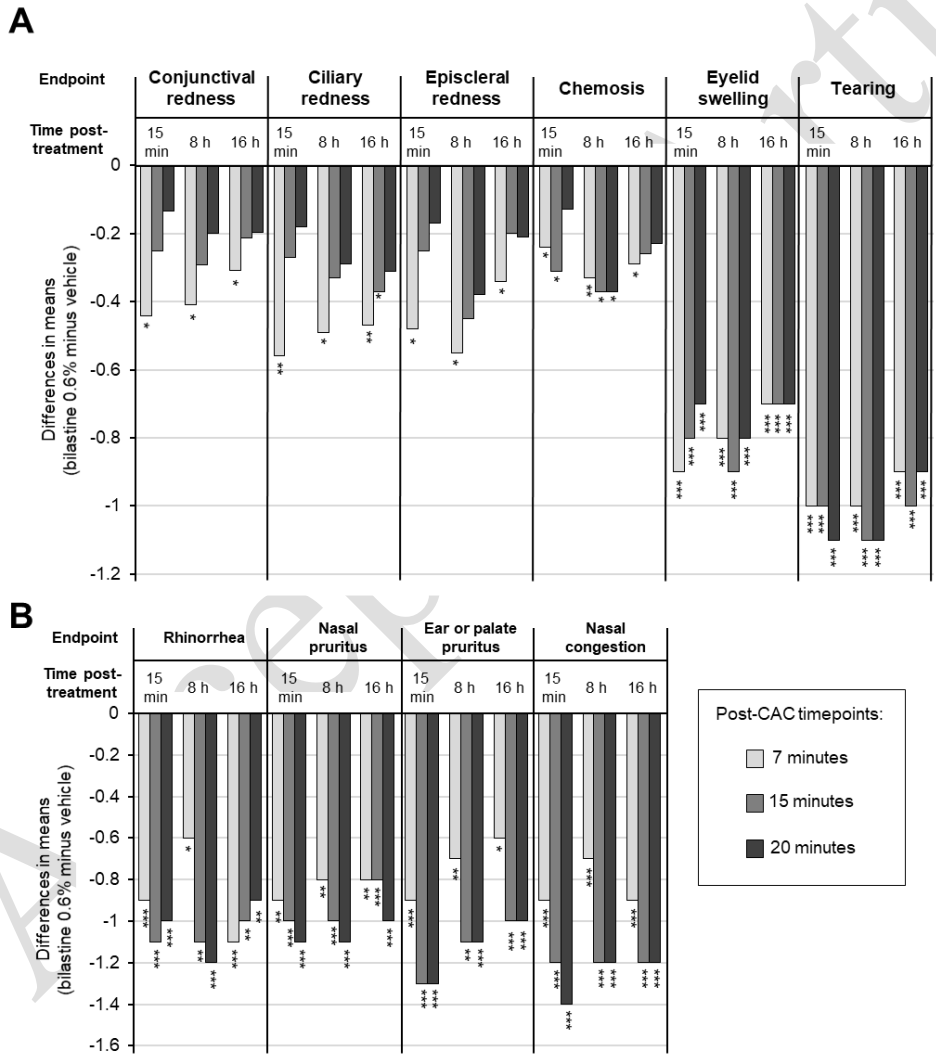

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Figure 5. Evaluation of the effects of allergen type in ocular itching at visits 4b (16 hours post-treatment), 5b (8 hours), and 6 (15 minutes) for the bilastine 0.6% group. Treatment differences calculated as bilastine 0.6% minus vehicle. Significance of differences was in all cases $p<0.001$, calculated using a two-sample t-test comparing the active treatment to vehicle.

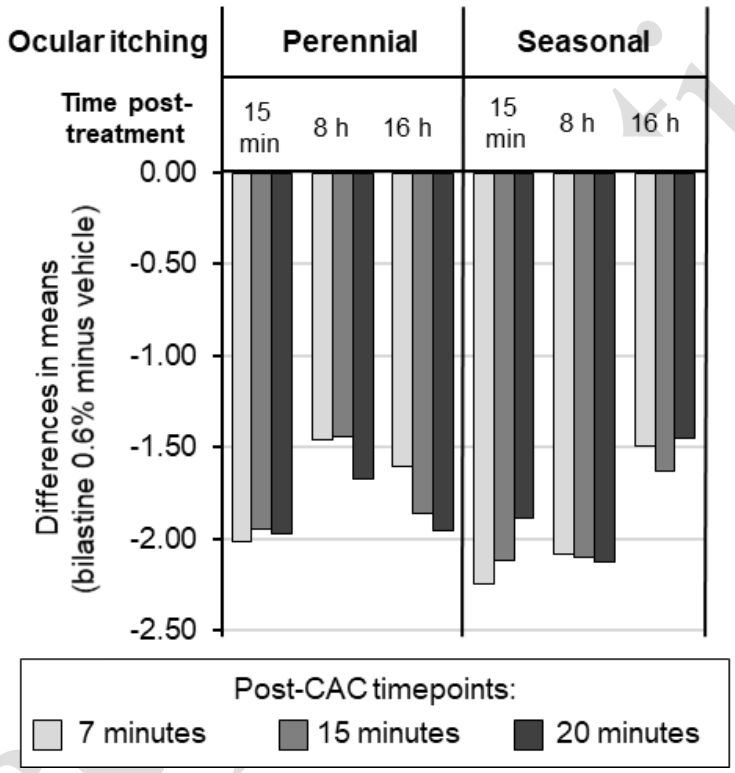

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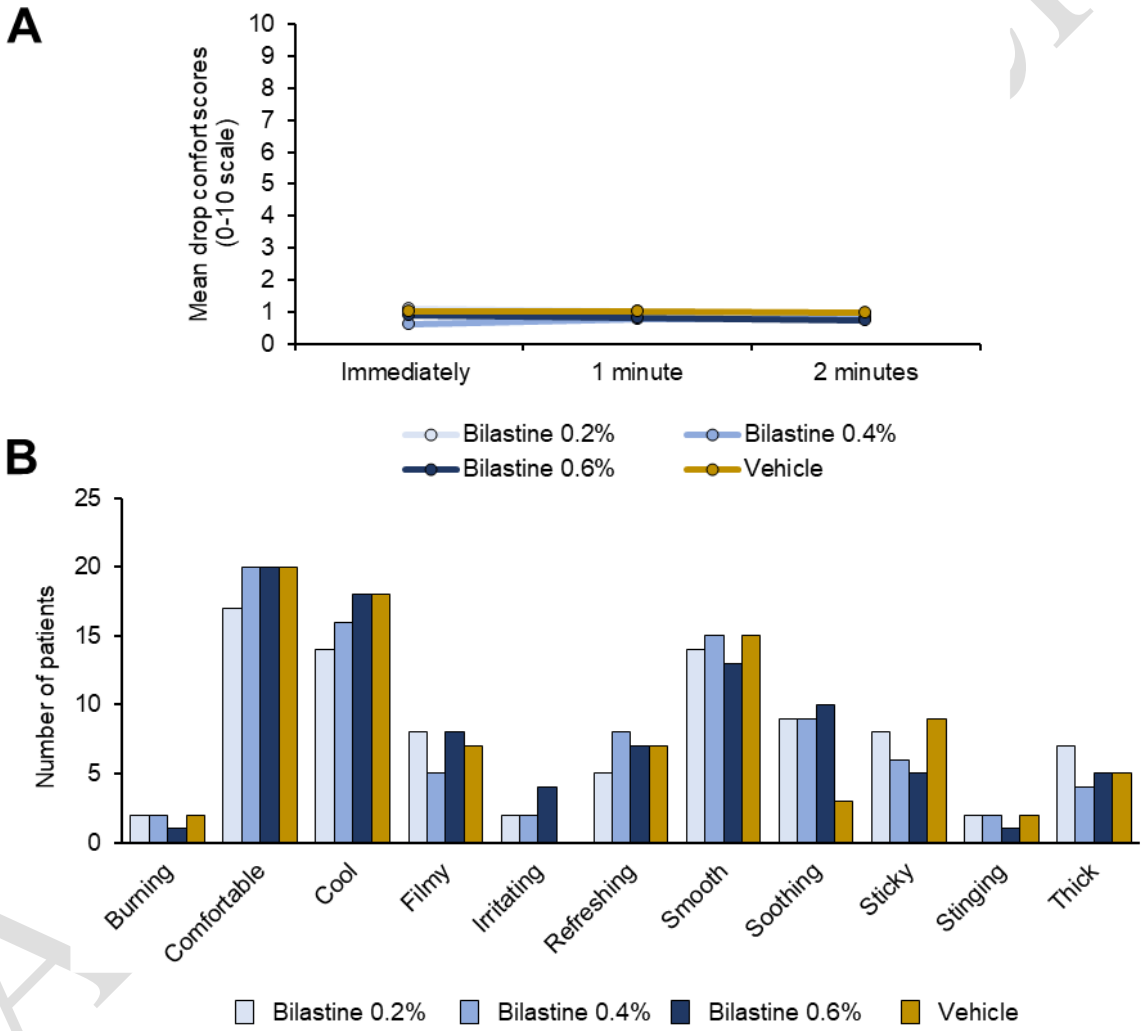
Figure 6. Evaluation of drop comfort. **A**, mean drop comfort scores immediately and 1 or 2 minutes after instillation. **B**, number of patients reporting specific descriptors of the drops. The Drop comfort questionnaire was administered 3 minutes post-instillation of study drug and asked subjects to choose three words that best described how each eye drop feels in both eyes.



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