Efficacy and Toxicity Evaluation of Bepotastine Besilate 1.5% Preservative-Free Eye Drops Vs Olopatadine Hydrochloride 0.2% Bak-Preserved Eye Drops in Patients with Allergic Conjunctivitis

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Purpose: To study the efficacy and toxic effects of bepotastine besilate 1.5% preservative-free (BB-PF) and olopatadine 0.2% BAK-preserved (OL-BAK) drops on the ocular surface of patients with allergic conjunctivitis.

Patients and Methods: Ninety-seven patients with allergic conjunctivitis diagnosis participated in a prospective, multicenter, randomized, double-blind, controlled, parallel-group clinical trial. Patients received either BB-PF (n=48) or OL-BAK (n=49), both administered once daily in the morning. The patients were followed for 60 days. Ocular itching was the primary outcome measure. Secondary outcomes included ocular symptoms, signs, and non-ocular symptoms associated with rhinoconjunctivitis. Conjunctival impression cytology (CIC) was performed to evaluate histopathological changes related to the toxic effects of preservatives.

Results: BB-PF treatment was associated with a 1.30 more probability of diminished ocular itching than OL-BAK (odds ratio (OR) =1.30; 95% CI=(0.96–1.7); p=0.086). No statistically significant differences were found between treatments in the resolution of other ocular symptoms or signs, except for tearing, which was superior in the BB-PF (OR=1.37; 95% (1.26–1.47); p<0.0001). BB-PF was superior in terms of the resolution of rhinorrhea (p=0.040) and nasal itching (p=0.037). After 60 days of treatment, the BB-PF group exhibited 2.0 times higher probability of having a lower Nelson scale score compared to the OL-BAK group (OR=2.00; 95% CI=(1.19–3.34); p=0.010).

Conclusion: Both medications presented a similar efficacy in terms of the resolution of ocular signs and symptoms associated with ocular conjunctivitis. BB-PF is superior in the resolution of non-ocular symptoms and safer for the ocular surface than OL-BAK.

Keywords: allergic conjunctivitis, bepotastine besilate, olopatadine, preservative-free, ocular surface, rhinoconjunctivitis

Introduction

Allergic conjunctivitis (AC) is the most common allergic ocular disorder, affecting approximately 20% of the global population. The prevalence of AC is region-dependent, and appears to be increasing worldwide. This pathology is associated with seasonal pollen sensitivity, although perennial forms are associated with exposure to animal dander, mites, and molds. AC is a type-1, IgE-mediated hypersensitivity immune reaction that occurs in individuals previously exposed to a specific allergen. The immune response involves the release of inflammatory mediators, including histamine, leukotrienes, bradykinin, prostaglandins, proteases, and cytokines, which contribute to the development of signs and symptoms. Histamines from degranulated mast cells are the principal immune mediators related to early allergic responses. This molecule binds to receptors (H1, H2, H3, and H4) on vascular endothelial cells, neuronal fibers,
goblet cells, immune cells, and conjunctival epithelium culminating in clinical manifestations of allergic conjunctivitis including redness, periocular swelling, chemosis, itching, and tearing. This is followed by a late phase that is manifested by pro-inflammatory mediators and the recruitment of immune cells including eosinophils and neutrophils.

The key to the treatments is histamine antagonists (also called antihistamines), which inhibit the action of histamine by blocking histamine receptors and, consequently, inhibiting clinical manifestations related to this mediator. Mast cell stabilizers inhibit mast cell degranulation and, consequently, the release of histamine by interrupting the normal chain of intracellular signals. The first line of treatment for this condition includes antihistamines that combine both mechanisms of action: dual-action antihistamines, which present an increased safety and efficacy profile compared with older topical agents used in the treatment of AC.

Bepotastine besilate is the latest-generation ophthalmic antihistamine with multiple mechanisms of action in both preclinical and clinical studies. This drug is a highly selective H1 receptor antagonist with potent mast cell-stabilizing action. Bepotastine besilate exerts its anti-inflammatory action through the inhibition of leukotriene B4 and the reduction and activation of eosinophil chemotaxis. It also inhibits the biosynthesis of proinflammatory IL-5 in vitro. The clinical efficacy and safety of bepotastine besilate twice a day (BID) have been demonstrated in several clinical studies. Recent studies suggest that the effect of bepotastine besilate 1.5% was maintained for up to 16 hr, so a posology of once a day in the morning can be proposed.

A large percentage of patients with AC also present nasal symptoms as a comorbidity, known as allergic rhinoconjunctivitis. In rhinitis epidemiology studies, it was found that approximately 90% of patients suffering from nasal symptoms also had ocular symptomatology. The conjunctiva and nasal mucosa share a similar epithelium, leading to a similar reactivity to the same allergens in both tissues. Some studies have supported that the use of bepotastine besilate 1.5% eye drops may have some effect on nasal symptoms associated with rhinoconjunctivitis because a significant proportion of the drug is expected to reach the nasal mucosa via the nasolacrimal duct.

The formulation under study is a new bepotastine besilate 1.5% preservative-free (PF) solution developed in a new multidose device called “Ophthalmic Squeeze Dispenser” (OSD, Aptar™ Pharma). The use of preservative-free ophthalmic formulations is necessary to prevent preservative-induced toxicity. Benzalkonium chloride (BAK), an ammonium quaternary compound widely used as a preservative in ophthalmic eye drops, is well known for its toxic effects. Although the adverse effects are more problematic with chronic exposure, they also manifest after exposure for as brief as 7 days.

Numerous documented cytotoxic effects of BAK exposure have been observed in ocular tissues. These effects include a reduction in corneal survival, trabecular meshwork (TM) impairment, decreased survival of ciliary epithelial cells, loss of conjunctival goblet cells, delayed corneal healing, lymphocyte infiltration of conjunctival epithelium and stroma, and an increase in inflammatory markers within ocular tissues. Furthermore, BAK exposure leads to various clinical manifestations that negatively impact the quality of life for patients. These include sensations of pain/discomfort, excessive tearing, a persistent feeling of a foreign body in the eye, subconjunctival inflammation/fibrosis, and signs of dry eye disease. These dry eye symptoms manifest as a reduced tear breakup time, diminished Schirmer test results, positive corneal and conjunctival staining, and a higher Ocular Surface Disease Index (OSDI) score.

To our knowledge, no prospective studies have established the effectiveness and safety of bepotastine besilate 1.5% PF once a day in comparison with olopatadine 0.2% BAK preserved under environmental exposure conditions.

Our study aims to evaluate the efficacy of this ophthalmic formulation on ocular symptoms and signs and non-ocular symptoms and to determine if there is any consequence on the histology of conjunctival epithelium after 60 days of treatment with bepotastine 1.5% PF compared to Olopatadine hydrochloride 0.2% BAK-preserved once a day in patients with allergic conjunctivitis.

**Materials and Methods**

**Design**

A prospective, multicenter, double-blind, randomized, parallel-group comparative trial was conducted between March 2021 and August 2022 in 4 public hospitals in Buenos Aires, Argentina.

This study was approved by the Institutional Review Board Ethics Committees (Comité de Ética en investigación Hospital Oftalmológico Santa Lucía, Comité de Ética en investigación Hospital Alta Complejidad El Cruce, Comité de...
Ética Biomédica del Complejo Médico Churruca Visca) and registered at clinicaltrials.gov under identifier NCT04776096. This study adhered to the tenets of the Declaration of Helsinki and was in accordance with The Code of Ethics of the World Medical Association. Informed consent was obtained from all participants after explaining the nature and possible consequences of the study.

Study Sample

Inclusion Criteria

Subjects had to meet the following inclusion criteria to be eligible for participation in the clinical trial: (1) at least 18 years of age; (2) provided written informed consent; (3) with allergic conjunctivitis diagnosis with subject-assessed ocular itching score ≥2 described as a mild continuous itch, can be localized, without a desire to rub, and physician-assessed ocular hyperemia score ≥2 described as moderate, more apparent dilation of blood vessels; vessel color is more intense; involves the majority of the vessel bed; (4) no use of contact lenses and other topical medications within the duration of participation; and (5) Intraocular pressure ≤18 mmHg in both eyes.

Exclusion Criteria

Potential participants were excluded if they (1) had undergone refractive surgery within 6 months before the start of the study; (2) had significant active systemic or ocular diseases (eg, glaucoma, blepharitis, or severe cardiovascular disease); (3) had used any eye medication in the last 15 days and/or had received anti-inflammatory drugs (corticosteroids and/or NSAIDs) and/or antihistamines orally or intravenously; or (4) had a known contraindication or sensitivity to the use of any study drugs or their components. (5) Women who are breastfeeding or pregnant.

Medication Under Study

Patients who met the eligibility criteria were randomly assigned according to a computer-generated randomization list to receive one of the two treatments under study: Bepotastine besilate 1.5% preservative-free (Traler® LC, Poen Laboratories, Argentina) or olopatadine hydrochloride 0.2% with 0.001% BAK (Patanol® S, Alcon Laboratories, Argentina) in 1:1 ratio. Each patient received two bottles of the same treatment for 60 days. Patients were instructed to instill either bepotastine besilate 1.5% or olopatadine 0.2% once daily (at approximately 8 am) for 60 days. Each treatment was provided in the packing, originally approved by the local sanitary authority but relabeled to maintain double masking.

Outcomes Measures

The primary efficacy endpoint was the patient-assessed ocular itching score at baseline and at 15, 30, 45, and 60 days after randomization.

As secondary endpoints, other ocular patient-assessed symptoms were evaluated, including tearing, eye burning, and foreign-body sensation. In addition, we evaluated physician-assessed ocular signs such as conjunctival hyperemia, chemosis, ocular secretion, and palpebral swelling.

Nasal symptoms, including congestion, pruritus, and rhinorrhea, were assessed. These endpoints were evaluated at baseline and 15, 30, 45, and 60 days after randomization.

Severity scales for all variables were based on a 4-point Likert Scale stratified as absent, mild, moderate, or severe. Ocular and non-ocular symptoms were assessed using a standardized questionnaire in which patients were required to check one of the four ordinal categories. Ocular signs were physician-assessed by ocular surface specialists and evaluated using slit-lamp biomicroscopy performed at each visit.

To evaluate ocular cytotoxicity, conjunctival impression cytology was performed at baseline and 30 and 60 days after randomization. Cytology was graded using Nelson’s classification. This classification considered four grades from 0 (normal epithelium) to stage III (absence of goblet cells and epithelial metaplasia). Stages 0 and I were considered normal epithelium and stages II and III abnormal conjunctival epithelium, as they did not show the presence of goblet cells.
Statistical Methods

The trial was analyzed by comparing patients randomized to bepotastine vs olopatadine, with this group serving as the referent. The primary outcome was analyzed using GEE to model the relationship between groups and itching grade over time, while accounting for within-subject correlation. Specifically, we used an ordinal logistic regression model to estimate the odds ratio (OR) of having a higher itching grade with bepotastine than olopatadine. An OR greater than 1.0 indicates a more favorable outcome on the symptom or sign score among patients randomized to bepotastine than to olopatadine. OR results with a 95% CI that did not include 1.0 were considered statistically significant.

The sample size calculated was 95 patients to detect an accumulative odds ratio of 0.41 in the absence of ocular itching on day 60, with a power of 0.80, and a two-tailed alpha of 0.05. Also, 15% of drop-out was considered.

All ordinal variables were analyzed using the GEE logistic ordinal regression. Demographic data were analyzed using the t-test for continuous variables and Pearson’s chi-square test for categorical data.

Data are presented as ORs and 95% confidence intervals (CIs) for the association between treatment group and symptom/sign grade for ordinal variables. Analyses were performed using IBM SPSS software (version 22.0, IBM Corp.).

Results

Study Population

A total of 101 patients were included in this study. Four of them were not included as they did not meet the inclusion criteria. A total of 97 patients from 4 ophthalmological centers were enrolled and randomized into treatment groups at the baseline visit, of which 75 completed all study visits (Figure 1).

The demographic characteristics (sex and age) of the patients were well-balanced between the treatment groups in the intention to treat (ITT) population. Pairwise comparisons between groups showed no statistically significant differences. The

![Figure 1 CONSORT Flow Diagram](https://doi.org/10.2147/OPTH.S431889)

Note: Flow-chart showing inclusion, randomization, and participation throughout the study.
median age of the enrolled population (n=97) was 43.2 years for bepotastine group and 45.0 for Olopatadine group, while most patients were women in both treatment groups: 68.1% for bepotastine group and 66.7% for olopatadine group.

**Ocular Symptoms**

Ocular itching: The degree of ocular itching decreased significantly over time in both groups of treatment (p<0.0001). Bepotastine besilate 1.5% PF administered once daily to patients with allergic conjunctivitis significantly reduced ocular itching, with a probability 1.30 times greater than that of olopatadine 0.2% BAK-preserved (odds ratio (OR) = 1.30; 95% confidence interval (CI) = (0.96–1.70); p = 0.086). After 60 days of treatment, 80.60% of patients in the bepotastine group completely resolved the main symptoms associated with allergic conjunctivitis, whereas 71.80% of patients in the olopatadine group completely resolved this symptom. None of the patients in the bepotastine group reported a moderate or severe degree of ocular itching after 60 days of treatment (Figure 2).

Tearing: The degree of tearing decreased significantly over time in both the treatment groups (p = 0.043). Bepotastine besilate 1.5% PF once a day reduced tearing with a probability of 1.37 times greater than olopatadine 0.2% BAK-

![Figure 2](image_url)

**Figure 2** (A) Ocular itching severity over the time in the Bepotastine group. (B) Ocular itching over the time in the Olopatadine Group.

**Notes:** Ocular itching was graded on a four points-Likert scale (absence, mild, moderate, severe), p = 0.086 for the GEE ordinal logistic regression. Each bar represents the percentage of patients in each degree of ocular itching by time.

**Abbreviation:** GEE, Generalized estimating equation.
preserved over time (OR = 1.37; 95% CI = (1.26–1.47); p < 0.0001). After 60 days of treatment, 80.55% of the patients in the bepotastine group had completely resolved tearing, while 65.80% had completely resolved this symptom in the olopatadine group (Figure 3).

Ocular burning: The degree of ocular burning decreased significantly over time in both the treatment groups (p < 0.0001). There were no statistically significant differences observed between the groups in terms of the resolution of ocular burning over time (OR = 0.78; 95% CI = (0.58–1.04); p = 0.096).

Foreign body sensation: The degree of foreign body sensation decreased significantly over time in both the treatment groups (p < 0.0001). No statistically significant differences were detected between the groups over time in the resolution of this symptom (OR = 0.86; 95% CI = (0.62–1.2); p = 0.390).

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Figure 3 (A) Tearing severity over the time in the Bepotastine group. (B) Tearing severity over the time in the Olopatadine group.

Notes: Tearing was graded on a four points-Likert scale (absence, mild, moderate, severe), p > 0.001 for the GEE ordinal logistic regression. Each bar represents the percentage of patients in each degree of tearing by time.

Abbreviation: GEE, Generalized estimating equation.
Ocular Signs
Conjunctival Hyperemia: Conjunctival hyperemia decreased significantly over time in both the treatment groups (p < 0.0001). No statistically significant differences were detected between groups over time in the resolution of this symptom (OR = 0.96; 95% CI = (0.76–1.23); p = 0.770).

Palpebral swelling: The severity of Palpebral swelling decreased significantly over time in both the treatment groups (p=0.003). No statistically significant differences were detected between the groups over time (OR = 1.16; 95% CI = (0.71–1.9); p = 0.548).

Ocular secretion: The degree of ocular secretion decreased significantly over time in both the treatment groups. There were no statistically significant differences between groups (OR = 0.54; 95% CI (0.28–1.52); p = 0.067).

Chemosis: After 15 days of treatment, all the patients who presented with this symptom at baseline showed complete resolution. No statistically significant differences were observed between the treatment groups (OR = 0.64; 95% CI = (0.11–3.6); p = 0.614).

Non-Ocular Symptoms
Nasal congestion: Nasal congestion severity decreased in patients who present with at least one non-ocular allergy symptom over time, with once-daily dosing in both treatment groups (p < 0.001). There were no statistically significant differences between the treatments in the reduction of the degree of nasal congestion over time (OR = 1.24; CI 95% = (0.82–1.89); p = 0.300) (Figure 4).

Nasal pruritus: The severity of nasal pruritus significantly decreased over time in both the treatment groups (p < 0.001).
Bepotastine 1.5% LC administered once daily to patients with allergic rhinoconjunctivitis significantly reduced nasal pruritus with a probability 1.45 times greater than olopatadine 0.2% with BAK (OR = 1.45; CI 95% = (1.25–2.05); p = 0.037) (Figure 4).

Rhinorrhea: The degree of rhinorrhea in patients who at baseline presented at least one non-ocular symptom of allergy decreased significantly over time with once-daily administration in both treatment groups (p < 0.001).
Bepotastine 1.5% PF administered once daily to patients with allergic rhinoconjunctivitis significantly reduced the degree of rhinorrhea, with a probability 1.42 times greater than that of olopatadine 0.2% with BAK (OR = 1.42; 95% CI = (1.17–1.98); p = 0.040) (Figure 4).

Complete resolution of non-ocular symptoms: The percentage of patients with total resolution of non-ocular symptoms increased significantly over time with once-daily dosing in both the treatment groups (p < 0.001). Bepotastine 1.5% PF, administered once daily to patients with allergic conjunctivitis, significantly alleviated non-ocular symptoms with 1.60 times higher probability compared to olopatadine 0.2% with BAK (OR = 1.60; 95% CI = 1.10–2.28; p = 0.014). At day 60 of treatment, approximately 90% of the patients treated with bepotastine besilate showed resolution of all nasal symptoms under analysis, whereas approximately 60% of the patients in the olopatadine group achieved complete resolution (p = 0.020) (Figure 5).

Figure 4 Foster plot for non-ocular symptoms (nasal pruritus, nasal congestion, and rhinorrhea).
Notes: Nasal pruritus, nasal congestion, and rhinorrhea were graded on a four points-Likert scale (absence, mild, moderate, severe). OR is shown by closed circles and whiskers represents the 95% CI. *p=0.037 **p=0.040.
Abbreviations: OR, Odds ratio; CI, confidence interval.
Conjunctival Impression Cytology
The histology of the conjunctival epithelium, classified using the Nelson scale, changed significantly over time in both treatment groups ($p = 0.001$).

Bepotastine 1.5% LC administered once daily improved the integrity of the conjunctival epithelium with a probability 2.00 times greater than that of olopatadine 0.2% with BAK (OR = 2.03; 95% CI = (1.19–3.34); $p = 0.010$). This toxic effect on the conjunctiva is likely due to the presence of BAK in the formulation. At day 60 after treatment, no citologies presented metaplasia in the bepotastine group, whereas three conjunctivas presented metaplasia in the olopatadine group (Figure 6).

Analyzing the data set as binary outcome (normal and abnormal conjunctiva), probability of presenting with a normal epithelium over time was 2.7 greater in the bepotastine group than in the olopatadine (OR = 2.72, 95% CI = (1.50–4.94); $p < 0.001$). After 60 days of treatment, the normal conjunctiva in the olopatadine group decreased by 27.4%, whereas in the bepotastine group, there was an improvement of 20.5% ($p = 0.006$) (Figure 7).

Safety
The safety population ($n=97$) was defined as subjects who received at least one dose of the test agent. Five ocular adverse events were reported: two in the bepotastine group (burning at instillation and palpebral allergic reaction) and three in the olopatadine group (periocular allergic reaction and viral conjunctivitis (2)). Four non-ocular adverse reactions reported by 3 of the 3 patients were possibly related to the treatment (dysgeusia in the bepotastine group and nausea and headache in the olopatadine group).

Discussion
Signs and symptoms of allergic conjunctivitis significantly decrease the quality of life and ability to function, sleep problems, decrease the ability to visual tasks, and social interactions. This leads to missed time at work, owing to visits to the doctor’s office and decreased productivity. Consequently, it is important to establish non-pharmacological, pharmacologically effective, and safe treatments.

Bepotastine besilate is a last-generation antihistamine drug with a high affinity for the $H_1$ receptor without any appreciable action on other receptors associated with undesirable effects such as histamine $H_3$, adrenergic ($\alpha_1$, $\alpha_2$, $\beta$), serotonin (5-HT$_2$), muscarinic, and benzodiazepine receptors. This multi-action antiallergic drug was first approved in Japan as an oral tablet formulation indicated to allergic rhinitis (AR) treatment. Clinical trials have investigated its safety and non-sedating effects when administered orally. In 2009, an ophthalmic formulation was developed and approved by

Figure 5 Complete resolution of non-ocular symptoms over the time by group of treatment.
Notes: Each bar represents the percentage of patients with complete non-ocular symptoms resolution by time. *$p=0.020$ for the GEE binary logistic regression.
Abbreviations: BB, Bepotastine besilate 1.5% ophthalmic solution; OL, Olopatadine 0.2% ophthalmic solution.
The efficacy and safety of bepotastine besilate 1.5% ophthalmic solution were studied previously using the CAC model of allergic conjunctivitis. These studies reported positive effects, including a reduction in ocular itching, which lasted for up to 8 hr, and even extended to 16 hr. Although the CAC model presents several advantages such as reproducibility, controlled allergen exposure, and the possibility of internal control when administered in the contralateral eye as a placebo solution, environmental models allow accurate assessment of chronic exposure to allergens with the normal fluctuating effects of geographic location, diversity in allergen sources, weather, and evidence of clinical improvements over several days or weeks, reflecting the real-life benefits of this therapeutic option.

Carr and collaborators published a natural exposure, a placebo-control clinical trial where the efficacy of bepotastine besilate 1.5% BID over 2 weeks was evaluated. In this trial, bepotastine resulted in efficacy and safe treatment of allergic conjunctivitis administered twice a day compared with placebo solutions.

We identified the need to compare bepotastine with other antiallergic treatments owing to the lack of published evidence. To the best of our knowledge, only two studies have compared bepotastine with other commercially available antiallergic ophthalmic solutions. Ayyappanavar et al compared bepotastine besilate 1.5% BID with olopatadine hydrochloride 0.2% and alcaftadine 0.25% administered once daily. Both antiallergic solutions were superior to Olopatadine analyzed by Total Ocular Symptom Scoring System (TOSS) after 14 days of treatments. McCabe et al assessed patient preferences for bepotastine besilate 1.5% administered twice daily and olopatadine 0.2% ophthalmic solution taken once daily in terms of patient-assessment relief and ocular comfort. Bepotastine besilate 1.5% BID provides better relief from ocular itching, nose itching, and morning and evening relief from ocular allergy symptoms than Olopatadine. However, there was no study that compared Bepotastine besilate 1.5% once a day vs any other antiallergic ophthalmic eye drop. In
our study, we conducted a comparative analysis between reduced dosage of Bepotastine besilate 1.5% and olopatadine 0.2%, both administered once daily. Olopatadine is a well-established dual-action antihistamine that has been widely used worldwide for several decades. It has demonstrated a similar efficacy and safety profile in resolving symptoms and signs associated with allergic conjunctivitis. Upon evaluating the signs and symptoms related to AC, we found no statistically significant differences between this and treatments, except for tearing, where bepotastine exhibited superior effectiveness compared to Olopatadine group over time.

Symptoms of both conditions, AC and AR, coexist in more than 80% of allergic patients.17 Since there are similarities between the allergic response in the conjunctival and nasal mucosa and the pharmacological agents used to treat both conditions are the same, suggesting that bepotastine may relieve both nasal and ocular allergic symptoms. Cavet et al analyzed results from two Phase III CAC trials and a two-week natural-exposure allergen Phase IV study17 where nasal outcomes were analyzed as secondary outcomes. In both studies, bepotastine besilate administered twice a day improved the resolution of nasal symptoms associated with allergic conjunctivitis, such as nasal congestion, rhinorrhea, and nasal pruritus. In our study, we evaluated the resolution of these symptoms with a reduced posology once daily. Compared with olopatadine 0.2% administered once daily, bepotastine was superior in the resolution of non-ocular symptoms, reaching approximately 30% more patients with complete resolution of these symptoms after 60 days of treatment.

It is important to emphasize the impact of preservatives on ocular surface integrity. Long term use of BAK-preserved ophthalmic solutions is widely known to cause several impairments in superficial and deep ocular tissues.20 In this study, the comparator group (olopatadine 0.2% ophthalmic solution) was preserved with BAK 0.01%. This is one of the highest

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**Figure 7 (A)** Percentage of normal conjunctivas over the time in the Bepotastine besilate group. **(B)** Percentage of normal conjunctivas over the time in the Olopatadine group.

**Notes:** Normal conjunctivas were cytologies classified as 0 or I by Nelson classification. p<0.001 for the GEE binary logistic regression.

**Abbreviation:** GEE, Generalized estimating equation.
concentrations of BAK used to prepare eye drops. As documented in several experimental and clinical trials, BAK was induced in the first stage of its toxic action histopathological changes that initially remain asymptomatic but could then evolve to more severe stages of ocular surface disease.\(^1\) In our investigation, we studied by conjunctival impression cytology, the histology of patients exposed to both formulations. We found that when patients were exposed to olopatadine hydrochloride 0.2% BAK-preserved, the integrity of the conjunctival epithelium decreased by 27.4% after 60 days of treatment, while 20.5% of patients treated with preservative-free bepotastine besilate recovered normal conjunctival histology.

Since adherence to treatment regimens is related to clinical benefits and patient wellness, it is possible to administer this modern antiallergic ophthalmic solution that presents additional benefits, such as resolution of nasal symptoms associated with rhinoconjunctivitis, in a reduced posology once a day.

In addition, formulations without preservatives may turn bepotastine besilate 1.5% PF into the next gold standard treatment for AC in the near future.

This research, however, is subject to some limitations. It would be more appropriate to add an objective measurement of allergic disease resolution as IgE tear levels, although in clinical practice the evaluation of resolution of symptoms and signs associated with this pathology is usually followed by ophthalmologist evaluation of signs and patient self-reporting of symptoms.

**Conclusion**
In conclusion, bepotastine besilate 1.5% administered once a day is at least as effective as olopatadine hydrochloride 0.2% BAK-preserved once a day in the reduction of ocular symptoms and signs associated with allergic conjunctivitis. Additionally, it offers a more comprehensive approach to treating rhinoconjunctivitis due to its superior effectiveness in resolving non-ocular symptoms. Moreover, it stands out in terms of safety, as it exhibits lower cytotoxicity and ensures the preservation of ocular surface integrity throughout allergic treatment, thanks to its preservative-free formulation.

**Abbreviations**
AC, Allergic Conjunctivitis; AR, Allergic Rhinitis; BAK, Benzalkonium Chloride; BID, Twice a day; CAC, Conjunctival allergen challenge model; CIC, Conjunctival impression cytology; OSD, Ophthalmic Squeeze Dispenser; PF, Preservative-Free; TOSS, total ocular symptom scoring system.

**Data Sharing Statement**
Any data besides what is included in the manuscript will be shared. Data will be accessible from the corresponding author at any time.

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