

Bepotastine besilate ophthalmic solution for the relief of nonocular symptoms provoked by conjunctival allergen challenge

Gail L. Torkildsen, MD*; Jon I. Williams, PhD†; James A. Gow, MD‡; Paul J. Gomes, MS‡; Mark B. Abelson, MD‡§||; and Timothy R. McNamara, PharmD‡; for the Bepotastine Besilate Ophthalmic Solutions Clinical Study Group

Background: Bepotastine besilate is a selective histamine₁-receptor antagonist and mast cell stabilizer with inhibitory effects on eosinophilic activity.

Objective: To evaluate the safety and efficacy of 1.5% bepotastine besilate ophthalmic solution in alleviating nonocular symptoms induced by a conjunctival allergen challenge (CAC), a clinical model of allergic conjunctivitis.

Methods: This was a single-center, double-masked, randomized, placebo-controlled clinical trial performed from March 1 to April 4, 2007. Patients 10 years or older with a history of allergic conjunctivitis and a reproducible, positive, clinical response to a CAC were eligible. Patients received either placebo or 1.5% bepotastine besilate, 1 drop in each eye. After 15 minutes, 8 hours, or 16 hours after dosing, a CAC was performed and patients evaluated nonocular symptoms using standardized grading scales.

Results: Seventy-one patients were enrolled in the study, and 66 comprised the per protocol population. A clinically meaningful reduction (≥ 1.0 unit) compared to placebo was achieved for rhinorrhea and nasal congestion at most time points after 1.5% bepotastine besilate instillation at 8 hours before a CAC test. Significant reductions ($P \leq .05$) in mean values were seen with 1.5% bepotastine besilate at 15 minutes and 8 hours after dosing for CAC-induced nasal congestion, rhinorrhea, ear or palate pruritus, nasal pruritus, and summed nonocular composite symptom (NOCS) scores and also at 16 hours after dosing for nasal congestion and rhinorrhea.

Conclusions: The 1.5% bepotastine besilate formulation produced statistically significant reductions after a CAC in individual nonocular symptoms and NOCS scores at onset of allergic response and for at least 8 hours after instillation, with the greatest reduction seen for nasal congestion and rhinorrhea.

Ann Allergy Asthma Immunol. 2010;105:57–64.

INTRODUCTION

Allergic conjunctivitis and allergic rhinitis commonly present as comorbidities and are often classified together as allergic

rhinoconjunctivitis.^{1–5} The early-phase allergic reaction, characterized by allergen-stimulated degranulation of IgE-bound mast cells^{6,7} and production of several proinflammatory mediators,^{8–11} induces ocular itching, conjunctival hyperemia (redness), nasal mucosal edema, tearing, and rhinorrhea.^{12,13} Many patients also experience a late-phase reaction 6 to 24 hours later characterized by eyelid swelling, ocular hyperemia,⁹ and nasal congestion.¹⁴ The interrelated ocular and nasal phenomena in allergic reactions suggest common pathophysiologic features facilitated by anatomical linkage via the nasolacrimal ducts. This raises the possibility of a single treatment option with an ophthalmic antihistamine to reduce both ocular and nonocular allergic symptoms.^{15,16}

Bepotastine besilate, (+)-(S)-4-{4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino} butyric acid monobenzenesulfonate (Figure 1), is an antihistamine that has been investigated in diverse preclinical and clinical studies.^{17–19} Bepotastine besilate is a specific histamine₁ (H₁)-receptor antagonist and mast cell stabilizer,^{17,20} with evidence of inhibitory action against allergen-stimulated eosinophilic migration and other proallergic mediators. Compared with placebo, oral bepotastine prevented an increase in eosinophils in bronchoalveolar lavage fluid in mice, and repeated administration of bepotastine significantly inhib-

Affiliations: * Andover Eye Associates, Andover, Massachusetts; † ISTA Pharmaceuticals Inc, Irvine, California; ‡ Ora Inc, Andover, Massachusetts; § Schepens Eye Research Institute; || Harvard Medical School, Boston, Massachusetts.

Disclosures: Dr. Torkildsen was the principal investigator and had no financial interest in the outcomes of the clinical trial. Drs Williams, Gow, and McNamara were responsible for the design and conduct of the clinical trial and are employees of the clinical trial sponsor, ISTA Pharmaceuticals Inc. Mr Gomes is an employee of and Dr Abelson is a consultant to Ora Inc, the contract research organization that conducted the clinical trial.

Previous Presentations: Data were presented in part at the Annual Meetings of the American College of Allergy Asthma & Immunology on November 9–10, 2008; Seattle, Washington; and on November 6–8, 2009; Miami Beach, Florida; and the Annual Scientific Session of the Western Society of Allergy, Asthma & Immunology on January 25–29, 2009; Maui, Hawaii.

Trial Registration: clinicaltrials.gov Identifier: NCT00424398.

Received for publication January 28, 2010; Received in revised form March 11, 2010; Accepted for publication April 11, 2010.

© 2010 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.04.005

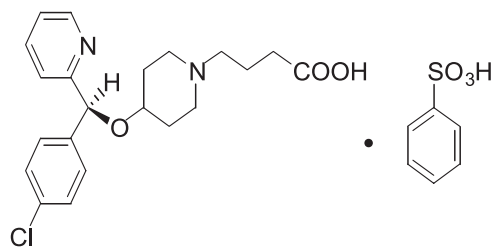


Figure 1. The chemical structure of bepotastine besilate.

ited peripheral blood eosinophilia from 1 to 3 days after challenge.²¹ A guinea pig model of allergic asthma suggested bepotastine besilate affects multiple allergic pathways by reducing airway resistance during immediate and late-phase allergic responses and suppressing platelet-activating factor-induced eosinophilic accumulation in the bronchoalveolar cavity.²² Studies with peripheral blood mononuclear cells from patients with Japanese cedar pollen allergy or dust mite allergy found that bepotastine suppressed antigen-induced production of interleukin 5, a growth and differentiation factor for eosinophils, in a concentration-dependent manner.^{23,24} The safety and efficacy of bepotastine besilate in preclinical studies led to clinical trials of an oral formulation in Japan.

An oral formulation of bepotastine besilate (Talion tablets) was formally approved by the Ministry of Health, Labour, and Welfare in Japan in July 2000 for the treatment of allergic rhinitis.²⁵ The clinical indication of oral bepotastine besilate was subsequently expanded and currently includes the treatment of pruritus accompanying urticaria and skin diseases (eczema, dermatitis, prurigo, and dermal pruritus).²⁵ In a postmarketing clinical surveillance program conducted in Japan, oral bepotastine besilate was clinically effective with minimal adverse events in pediatric patients with allergic rhinitis.²⁶ Subsequent clinical studies also have provided evidence that oral bepotastine besilate can relieve nonocular symptoms in allergic rhinitis patients, including nasal congestion, with a favorable risk-benefit profile.^{27,28} The clinical efficacy seen in Japan with bepotastine besilate led to the initiation of an ophthalmic formulation clinical development program in the United States for treating allergic conjunctivitis using the conjunctival allergen challenge (CAC) model of allergic conjunctivitis.

The CAC is a standardized, reproducible, clinical method of inducing ocular and nonocular signs and symptoms associated with allergic conjunctivitis.²⁹ The CAC model is valuable as a clinical approach because it attempts to isolate clinical trial results from environmental variables (eg, weather, pollen counts, and within- and between-subject variability) that may hinder reproducibility in a seasonal allergy investigation.^{30,31} The CAC model has been used to investigate the effects of ophthalmic antiallergic medications on nasal symptoms after an ocular allergen challenge^{4,6,32–34} and, conversely, to evaluate the efficacy of intranasal antiallergic medications on ocular symptoms.⁴ The CAC model results for several

antiallergic ophthalmic agents intended to alleviate the signs and symptoms of allergic conjunctivitis have supported successful new drug applications to the US Food and Drug Administration (FDA).^{35–38}

A single-site, randomized, double-masked, phase 3 CAC clinical trial in patients with a documented history of allergic conjunctivitis demonstrated that 1.5% bepotastine besilate ophthalmic solution was effective compared with placebo in the control of allergen-induced ocular itching for at least 8 hours after dosing.³⁹ These ophthalmic clinical results were affirmed in a separate multisite CAC trial and led to the FDA approval of 1.5% bepotastine besilate ophthalmic solution (Bepreve) in 2009 to treat ocular itching associated with allergic conjunctivitis.

Because of the range of clinical symptoms reported by patients with allergic conjunctivitis or rhinoconjunctivitis, we concurrently tested a secondary end point hypothesis in the single-site CAC trial. Specifically, we asked whether 1.5% bepotastine besilate might decrease CAC-induced nonocular symptoms compared with placebo at 15 minutes, 8 hours, or 16 hours after ocular dosing. The nonocular symptoms examined were rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus.

METHODS

Study Design

The clinical protocol was approved by an institutional review board (IntegReview, Austin, Texas) before initiation of study procedures. The clinical trial was conducted in accordance with good clinical practices, the World Health Organization Declaration of Helsinki 1996, and the Health Insurance Portability and Accountability Act. All patients read and signed an informed consent document for both treatment and participation in this clinical trial before initiation of any study-related procedures. Between March and April 2007, patients were enrolled at a single clinical site in Andover, Massachusetts.

Inclusion Criteria

The key inclusion criteria were age of 10 years or older; written informed consent at visit 1 before any study procedures; a negative pregnancy test result (from all females of childbearing potential, who also agreed to use a medically acceptable form of birth control during the study duration); a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, grasses, ragweed, and/or trees within the prior 24 months; a best-corrected visual acuity of 0.7 logMAR or better; and avoidance of disallowed medications and contact lens wear for the designated period.

Patients were required to have positive bilateral CAC reactions for ocular itching and conjunctival redness within 10 minutes of allergen instillation at 2 screening visits. This meant that patients received allergen to which they were most sensitive according to their skin test results at successively increasing concentrations of test allergen until they demonstrated adequate ocular itching and conjunctival hyperemia

scores to qualify for enrollment. The test allergens included grasses (eg, ragweed, Kentucky bluegrass, or rye grass), tree pollen (birch or oak), and cat hair or cat dander. Patients were challenged with allergen at visit 1 and again at visit 2 to confirm the allergic reaction.

Exclusion Criteria

The key exclusion criteria were any known contraindications to study medications(s) or their components, an ocular condition (eg, pterygium) or systemic illness that could have affected safety or trial parameters, ocular surgery within 3 months of visit 1 or refractive surgery within 6 months, signs or symptoms of active allergic conjunctivitis at the start of any visit, use of disallowed medications during the designated period, use of an investigational drug or device within 30 days of the study or concurrent enrollment in another investigational trial, or pregnancy, planning a pregnancy, lactating, or not using a medically acceptable form of birth control.

Study Medications

The test agents were formulated, packaged, and labeled by Alliance Medical Products Inc (Irvine, California). Both 1.5% bepotastine besilate and placebo (vehicle) were identically formulated as colorless ophthalmic solutions, and the vial packaging was identical for both study medications. The content of the vials containing test agent was masked to the patients and investigators, and labeling of the test agents was identical except for the patient number.

Study Protocol

The clinical trial consisted of a total of 5 visits, with enrolled patient participation occurring during the period of March 1 to April 4, 2007. Examiners who conducted the clinical trial procedures had prior experience with the CAC method.²⁹ The target study population consisted of patients with a positive reaction in both eyes to a CAC at visit 1 (day 0) and visit 2 (day 7), defined as scores of 2.0 units or greater on standardized 0- to 4-unit scales (0.5-unit steps allowed) for the primary efficacy variables of ocular itching and conjunctival hyperemia.^{35,40} Ocular itching and conjunctival hyperemia are considered the hallmark symptom and sign, respectively, of allergic conjunctivitis. Secondary ocular signs and symptoms evaluated in the CAC trials included ciliary and episcleral hyperemia, chemosis, mucous discharge, tearing, and eyelid swelling. Objective nonocular signs were not evaluated in this clinical trial. The secondary nonocular symptoms evaluated (nasal congestion, rhinorrhea, nasal pruritus, and ear or palate pruritus) were each quantified on a 0- to 4-unit pre-specified grading scale (0 indicating none and 4 indicating severe; 0.5-unit steps not allowed), and a summed nonocular composite symptom (NOCS) score was calculated on a 0- to 16-unit scale. Enrolled patients were not required to exhibit minimum scores for the CAC-induced, nonocular, secondary efficacy symptom variables during screening.

Approximately 35 patients were assigned at visit 3 (day 21) to each of the 1.5% bepotastine besilate and placebo treatment groups in a 1:1 randomization. A CAC test for each

enrolled patient was performed 16 hours after bilateral test agent dosing at visit 3, 8 hours after dosing at visit 4 (day 35), and 15 minutes after dosing at visit 5 (day 49). If necessary, currently marketed over-the-counter antiallergy eye drops (Visine-A or Naphcon-A) were administered to patients at the end of each visit after all evaluations were completed.

Safety evaluations for distance visual acuity using an Early Treatment Diabetic Retinopathy Study eye chart, slitlamp biomicroscopy, and recording of adverse events were performed at every study visit. Pregnancy tests (for females), intraocular pressure measurements, and dilated funduscopy were performed at visit 1 and for patients when exiting the study at visit 5. Updating of medical histories was completed at each of study visits 2 through 5.

Efficacy Analyses

A sample size of approximately 30 to 35 patients per treatment group was targeted, a number expected to have greater than 85% power to detect a true mean grade difference of 1.0 unit between 2 groups assuming an SD of 1.0 unit. Efficacy analyses were completed on the per protocol population who exhibited no major protocol violations as the primary analysis population. Clinical success was defined as achieving clinically and statistically significant improvement for an efficacy variable at visit 5 and at visit 3 and/or visit 4. Clinical significance was prospectively defined as a 1.0-unit change or greater in mean values (placebo – active) for most time points at a study visit.

Making no assumption about the treatment data distributions, the Wilcoxon rank sum test was used in comparisons of median values for the nonocular symptoms of ear or palate pruritus, nasal pruritus, nasal congestion, and rhinorrhea and for the NOCS scores (both eyes averaged) between 1.5% bepotastine besilate and the placebo treatment groups at each observation time point. Statistical significance at a time point was defined as $P \leq .025$ at visits 3 and 4 and $P \leq .05$ at visit 5, adjusting each nonocular end point for multiple comparisons between visits 3 and 4 using conservative Bonferroni adjustments. Statistical significance at a study visit for nonocular efficacy variables required demonstration of significance at most time points. Post hoc statistical calculations for differences in proportions of patients with improvement in rhinorrhea compared with baseline values after placebo and 1.5% bepotastine besilate instillation applied z statistics.⁴¹

RESULTS

Patient Disposition

A total of 71 patients (36 in the placebo group and 35 in the 1.5% bepotastine besilate group) were assigned to groups according to a computer-generated randomization list. Four patients discontinued participation in the clinical trial, including 3 patients lost to follow-up before visit 5 and 1 patient who discontinued because of unacceptable baseline redness at visit 5. A fifth patient completed the clinical trial but was subsequently determined to be ineligible for evaluation because of an exclusionary pterygium at visit 3. The per pro-

Table 1. Demographics of the Intent-to-Treat Population Treated With Placebo or 1.5% Bepotastine Besilate Ophthalmic Solution^a

Demographic	Placebo (n = 36)	1.5% Bepotastine besilate (n = 35)	P value
Age, y			.31
Mean (SD)	40.9 (11.4)	44.3 (16.0)	
Range	13.0–65.0	11.0–73.0	
Age category, y			
>18	34 (94.4)	33 (94.3)	
≤18	2 (5.6)	2 (5.7)	
Sex			.81
Female	17 (47.2)	18 (51.4)	
Male	19 (52.8)	17 (48.6)	
Race			.15
White	33 (91.7)	31 (88.6)	
African American	1 (2.8)	1 (2.9)	
Asian	2 (5.6)	0 (0.0)	
Other	0 (0.0)	3 (8.6)	
Iris color			.72
Blue	12 (33.3)	11 (31.4)	
Brown	19 (52.8)	17 (48.6)	
Green	2 (5.6)	1 (2.9)	
Hazel	3 (8.3)	6 (17.1)	

^a Data are presented as number (percentage) of patients unless otherwise indicated.

tol population was therefore a total of 66 patients (34 in the placebo group and 32 in the 1.5% bepotastine besilate group).

Patient Demographics

Mean (SD) patient ages were 40.9 (11.4) years in the placebo group and 44.3 (16.0) years in the 1.5% bepotastine besilate

group. The numbers of patients stratified by sex, race, and iris color were well balanced between the treatment groups ($P > .15$ in all categories; Table 1).

Nonocular Effectiveness Assessments

Statistical significance ($P \leq .01$, Wilcoxon rank sum test) was seen for reduced rhinorrhea and nasal congestion for 1.5% bepotastine besilate compared with placebo at all time points when 1.5% bepotastine besilate was dosed 15 minutes, 8 hours, or 16 hours before a CAC (Table 2). In general, the effectiveness at a study visit tended to be more pronounced at the peak allergen reaction time, which was 15 minutes after a CAC as estimated from placebo treatment group data. The effect was more pronounced for reduction in rhinorrhea at 8 hours after dosing (Figure 2) than for reduction in nasal congestion at 8 hours (Figure 3). A 1.0-unit difference in mean values (placebo – active) was also seen at the 15-minute post-CAC observation for rhinorrhea during the 16-hour duration of action CAC test, but this result did not meet the standard of most time points required to be clinically significant.

Statistical significance ($P \leq .025$ for visits 3 and 4 and $P \leq .05$ for visit 5) was found at most time points after CAC test agent dosing 15 minutes and 8 hours before a CAC test for both nasal pruritus and ear or palate pruritus but not for either of these nonocular symptoms when test agents were dosed 16 hours before a CAC test (Table 3). However, clinical success was not seen for either nasal pruritus or ear or palate pruritus at any study visit (Table 3). The sustained clinical benefit in reduced nasal pruritus and ear or palate pruritus for at least 8 hours after dosing was slightly greater at the CAC test 8 hours after dosing than at the CAC test 15

Table 2. Mean Rhinorrhea and Nasal Congestion Scores for Per Protocol Patients at CAC Tests Conducted 15 Minutes, 8 Hours, or 16 Hours After Dosing

	Rhinorrhea scores		Nasal congestion scores	
	Placebo	1.5% Bepotastine besilate	Placebo	1.5% Bepotastine besilate
Onset of action CAC test				
No. of patients	34	30	34	32
7 min	1.00	0.31 ^a	0.97	0.41 ^b
15 min	1.09	0.50 ^b	1.18	0.41 ^a
20 min	0.97	0.41 ^b	1.24	0.41 ^a
8-Hour duration of action CAC test				
No. of patients	31	27	31	27
7 min	1.00	0.04 ^{a,c}	1.00	0.07 ^a
15 min	1.68	0.11 ^{a,c}	1.29	0.15 ^{a,c}
20 min	1.42	0.19 ^{a,c}	1.26	0.19 ^{a,c}
16-Hour duration of action CAC test				
No. of patients	34	32	34	32
7 min	1.09	0.37 ^a	1.06	0.33 ^a
15 min	1.44	0.43 ^{a,c}	1.35	0.50 ^a
20 min	1.29	0.57 ^b	1.24	0.57 ^b

Abbreviation: CAC, conjunctival allergen challenge.

^a $P \leq .001$.

^b $P \leq .01$.

^c Difference (placebo – bepotastine besilate) of 1.0 unit or greater.

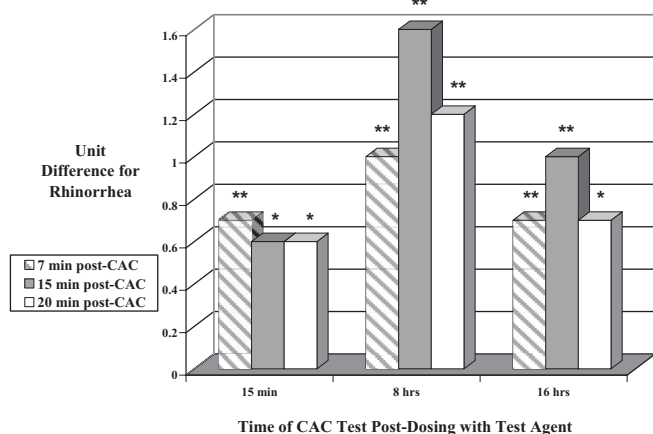


Figure 2. The difference in mean rhinorrhea grades as a function of time after dosing with the test agent. The rhinorrhea grade differences are expressed as differences in mean values (placebo – 1.5% bepotastine besilate) at each observation time point. A 1.0-unit difference at most times during a study visit is considered clinically significant. * $P \leq .01$, ** $P \leq .001$. CAC indicates conjunctival allergen challenge.

minutes after dosing, suggesting that the benefit for these nonocular symptoms was not necessarily an immediate response to drug exposure.

A post hoc analysis was performed for the degree of improvement by patient in rhinorrhea during CAC tests at visits 3, 4, and 5 compared with baseline visit 2. This analysis was performed for rhinorrhea because it represented the strongest nonocular response in this CAC trial to 1.5% bepotastine besilate. The proportion of patients achieving at least a 1.0- or 2.0-unit improvement compared with their baseline data was substantially higher for those patients instilling 1.5% bepotastine besilate than for those instilling

Table 3. Difference in Mean Scores (Placebo – 1.5% Bepotastine Besilate) for Nasal Pruritus, Ear or Palate Pruritus, and Nonocular Composite Symptoms (NOCS)

Time of post-CAC grading	Time after dosing before CAC test		
	15 min	8 h	16 h
Nasal pruritus			
7 min	0.5 ^a	0.6 ^a	0.4
15 min	0.8 ^a	0.9 ^a	0.5 ^b
20 min	0.4 ^a	0.7 ^a	0.4 ^c
Ear and palate pruritus			
7 min	0.5 ^a	0.5 ^a	0.3
15 min	0.5 ^b	1.0 ^a	0.5
20 min	0.5 ^c	0.6 ^b	0.2
NOCS			
7 min	2.3 ^a	3.0 ^a	2.1 ^a
15 min	2.7 ^a	4.6 ^a	2.9 ^a
20 min	2.3 ^a	3.6 ^a	2.0 ^b

Abbreviation: CAC, conjunctival allergen challenge.

^a $P \leq .01$.

^b $P \leq .02$.

^c $P \leq .05$.

placebo, although there was a considerable placebo response (Figure 4). The greatest difference between placebo and 1.5% bepotastine besilate in percentage of patients experiencing at least a 1.0-unit improvement was seen for a CAC test given 8 hours after dosing with the test agent.

The NOCS score was the aggregate response of patients on CAC tests to all nonocular clinical manifestations of allergic conjunctivitis. A NOCS score has no simple validated clinical correlate in allergic conjunctivitis, although it resembles the total nasal symptom score used as a global indicator of therapeutic response in environmental studies of agents to treat allergic rhinitis.⁴² Improvement in NOCS score was

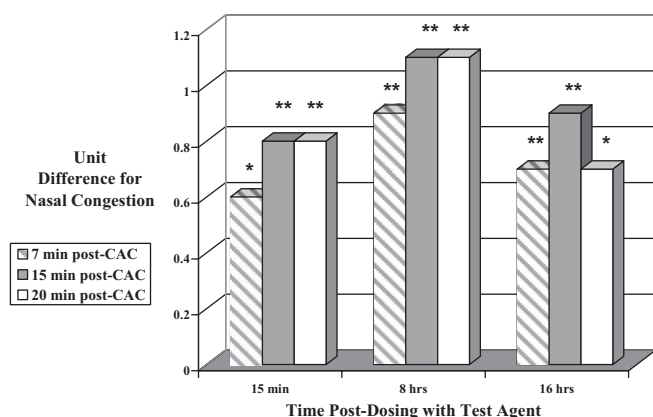


Figure 3. The difference in mean nasal congestion grades as a function of time after dosing with the test agent. Nasal congestion grade differences are expressed as differences in mean values (placebo – 1.5% bepotastine besilate) at each observation time point. A 1.0-unit difference at most times during a study visit is considered clinically significant. * $P \leq .01$, ** $P \leq .001$. CAC indicates conjunctival allergen challenge.

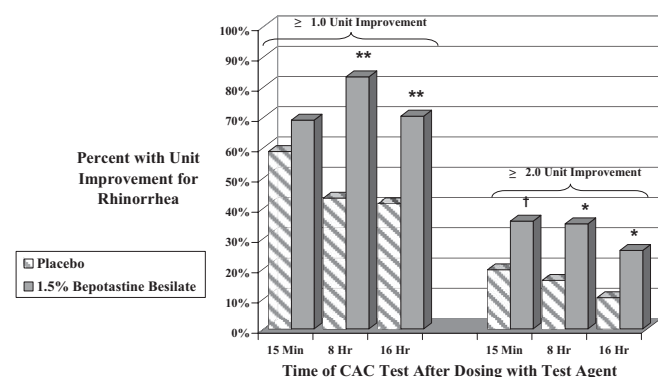


Figure 4. The percentage of rhinorrhea observations with a greater than 1.0-unit or 2.0-unit improvement compared with the screening baseline values. Observations are shown using data collected by eye and pooled across all time points at a study visit. Statistical significance relative to placebo is as indicated. * $P = .004$; ** $P < .0001$; † $P = .009$. CAC indicates conjunctival allergen challenge.

significant ($P \leq .01$) with 1.5% bepotastine besilate compared with placebo at most time points for at least 16 hours after dosing (Table 3). The clinical differences and statistical significance for the effect on NOCS scores was greatest at the CAC test 8 hours after dosing with test agent.

Safety Assessments

Patients who received 1.5% bepotastine besilate did not experience any changes from baseline in visual acuity, slitlamp biomicroscopy, intraocular pressure, or dilated funduscopy. The most common treatment-related adverse event was a mild taste on instillation, with 3 occurrences in patients who instilled 1.5% bepotastine besilate and none in the placebo treatment group. One 1.5% bepotastine besilate patient and 2 placebo patients reported eye irritation, and 1 patient reported a foreign-body sensation after instilling placebo. No serious or severe adverse events were reported in the safety population.

DISCUSSION

This clinical trial provides evidence that 1.5% bepotastine besilate, when dosed before a CAC, significantly and safely prevents nonocular symptoms compared with placebo for at least 8 hours after dosing. The clinical effects on rhinorrhea, nasal congestion, nasal pruritus, palate or ear pruritus, and NOCS scores were evident within 15 minutes of a CAC and were sustained when patients were challenged 8 hours after dosing and, for rhinorrhea and nasal congestion, at 16 hours after dosing. The 8-hour duration data provided the strongest and most consistent evidence of nonocular symptomatic relief. The 1.5% bepotastine besilate test agent also was safe and well tolerated without any reports of serious or severe adverse events. Overall, this clinical trial has provided additional evidence of the safety profile and diverse nonocular clinical effectiveness of bepotastine besilate.

Bepotastine besilate acts as a selective H_1 -receptor inhibitor that stabilizes mast cells and inhibits activation of eosinophils.^{17,20,43} Multiple clinical studies of bepotastine besilate given orally have demonstrated its safety and efficacy in allergic rhinitis and urticaria.^{18,19,27,28} A small, uncontrolled study of oral bepotastine besilate in patients with seasonal allergic rhinitis found trends for improvement in sneezing, nasal discharge, and nasal congestion.⁴⁴ The 1.5% bepotastine besilate formulation discussed herein has also demonstrated reduction of ocular itching in allergic conjunctivitis.³⁹ The additional clinical benefits of bepotastine besilate in reducing rhinorrhea, nasal congestion, nasal pruritus, palate or ear pruritus, and NOCS scores parallels the systemic version of bepotastine as a broadly effective antihistamine capable of diminishing both ocular and nonocular allergic responses.

Although systemic antihistamines may be used to control nasal symptoms, their nonspecific histamine activity may include antimuscarinic effects that can cause drowsiness, reduced tear volume, possible dry eye symptoms, and decreased flow dynamics,^{42,45,46} which may lead to increasing ocular discomfort. An ophthalmic antiallergic agent also will minimize systemic adverse events compared with oral agents.^{6,15,16}

The improved adverse event profile with topical H_1 -specific agents suggests a treatment paradigm shift for topical targeted therapy may be applicable for allergic rhinoconjunctivitis. For example, one clinical study using conjunctival and nasal allergen challenge models showed mometasone nasal spray and an antihistamine ophthalmic solution to be more effective than oral fexofenadine alone.⁴ A separate CAC study demonstrated fluticasone nasal spray and an antihistamine ophthalmic solution to be more effective than fluticasone and oral fexofenadine for treating allergic rhinoconjunctivitis.⁷ On the basis of the clinical results of 1.5% bepotastine besilate for both ocular³⁹ and nonocular signs and symptoms of allergic conjunctivitis, a single topical therapy can be considered another treatment option for patients with allergic rhinoconjunctivitis.

Using both nasal allergen challenge and CAC may have been more representative of the nasal and ocular signs and symptoms experienced in the environment. It has been previously shown that both nasal allergen challenge and CAC induce similar patterns of allergic response and effectiveness of clinical treatment for nasal and ocular allergic reactions.⁴ Therefore, the nasal symptom results using the CAC method can be considered to mimic the nasal symptoms of a nasal allergen challenge, which in the present CAC studies satisfactorily induced nonocular (particularly nasal) allergic symptoms and provided evidence of effective improvement after treatment with 1.5% bepotastine besilate. Performing both a nasal allergen challenge and a CAC in a future clinical study would be of interest to confirm this supposition. Objective measurements of clinical benefit for nasal allergic symptoms in patients with perennial allergic rhinitis using an oral formulation of bepotastine besilate have been previously described.⁴³ However, the absence of any objective measures of reduced nasal allergic response, either of increased nasal patency or decreased inflammatory cell infiltrates (eg, eosinophils and neutrophils), in this CAC clinical study with 1.5% bepotastine besilate suggests additional clinical investigations are needed to validate the subjective findings we have described.

In conclusion, 1.5% bepotastine besilate dosed bilaterally was safe with statistically significant positive effects on nonocular symptoms using the CAC model of allergic conjunctivitis. The pathophysiologic similarity of allergic conjunctivitis and allergic rhinitis may account for the clinical effectiveness for 1.5% bepotastine besilate to reduce both ocular and nonocular manifestations of allergic conjunctivitis. These data in a model of allergic conjunctivitis support the use of 1.5% bepotastine besilate in patients with allergic conjunctivitis and seasonal allergic rhinitis. To confirm this conclusion and to enhance understanding of the course of effects on nonocular symptoms, environmental clinical studies of 1.5% bepotastine besilate in patients with predefined comorbidities of seasonal allergic rhinitis and allergic conjunctivitis should be considered.

ACKNOWLEDGMENTS

We gratefully acknowledge Kathryn S. Kennedy, MSc, of Statistics and Data Corporation (Tempe, Arizona) for statistical analyses; Annie C. Plumer, BS, of Ora, Inc. (Andover, Massachusetts) for assistance in editing the manuscript; Welyn C. Bui, PharmD; and Laura L. Kososki, MD, MBA of ISTA Pharmaceuticals, Inc. (Irvine, California) for manuscript review. Japanese translations were provided by Senju Pharmaceutical Co., Ltd., Osaka, Japan; LinguaLinx, New York, New York; and TransPerfect, New York, New York.

APPENDIX

Members of the Bepotastine Besilate Ophthalmic Solutions Clinical Study Group included:

Stacey L. Ackerman, MD, Philadelphia Eye Associates, Philadelphia, Pennsylvania;

Mark T. Bergmann, MD, Eye Care Associates of Greater Cincinnati, Inc., Cincinnati, Ohio;

Jung T. Dao, MD, Cornea Consultants of Arizona, Phoenix, Arizona;

Fred K. Kurata, MD, East West Eye Institute, Los Angeles, California;

Thomas T. Macejko, MD, Eye Care Associates of Greater Cincinnati, Inc., Fairfield, Ohio;

Eugene B. McLaurin, MD, Total Eye Care, Memphis, Tennessee;

Edward J. Meier, MD, Eye Care Associates of Greater Cincinnati, Inc., Mason, Ohio;

Clifford M. Michaelson, MD, Andover Eye Associates, Andover, Massachusetts;

Thomas K. Mundorf, MD, Mundorf Eye Center, Charlotte, North Carolina;

Eugene E. Protzko, MD, Seidenberg Protzko Eye Associates, Bel Air, Maryland;

Tushina A. Reddy, MD, Ophthalmic Associates, Las Vegas, Nevada;

Gail L. Torkildsen, MD, Andover Eye Associates, Andover, Massachusetts.

REFERENCES

1. Gradman J, Wolthers OD. Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic. *Pediatr Allergy Immunol.* 2006;17:524–526.
2. Prenner BM, Schenkel E. Allergic rhinitis: treatment based on patient profiles. *Am J Med.* 2006;119:230–237.
3. Kosirukvongs P, Visitsunthorn N, Vichyanond P, Bunnag C. Allergic conjunctivitis. *Asian Pac J Allergy Immunol.* 2001;19:237–244.
4. Spangler DL, Abelson MB, Ober A, Gomes PJ. Randomized, double-masked comparison of olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. *Clin Ther.* 2003;25:2245–2267.
5. Paulsen FP, Foge M, Thale AB, Tillmann BN, Mentlein R. Animal model for the absorption of lipophilic substances from tear fluid by the epithelium of the nasolacrimal ducts. *Invest Ophthalmol Vis Sci.* 2002;43:3137–3143.
6. Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal allergic rhinoconjunctivitis in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. *Clin Ther.* 2003;25:1975–1987.
7. Lanier BQ, Abelson MB, Berger WE, et al. Comparison of the efficacy of combined fluticasone propionate and olopatadine versus combined fluticasone propionate and fexofenadine for the treatment of allergic rhinoconjunctivitis induced by conjunctival allergen challenge. *Clin Ther.* 2002;24:1161–1174.
8. Mygind N, Nielsen LP, Hoffmann HJ, et al. Mode of action of intranasal corticosteroids. *J Allergy Clin Immunol.* 2001;108(suppl 1):S16–25.
9. Bacon AS, Ahluwalia P, Irani AM, et al. Tear and conjunctival changes during the allergen-induced early- and late-phase responses. *J Allergy Clin Immunol.* 2000;106:948–954.
10. Gelfand EW. Inflammatory mediators in allergic rhinitis. *J Allergy Clin Immunol.* 2004;114(suppl 5):S135–S138.
11. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *N Engl J Med.* 1990;323:1033–1039.
12. Abelson MB, Smith L, Chapin M. Ocular allergic disease: mechanisms, disease sub-types, treatment. *Ocul Surf.* 2003;1:38–60.
13. Hansen I, Klimek L, Mosges R, Hormann K. Mediators of inflammation in the early and the late phase of allergic rhinitis. *Curr Opin Allergy Clin Immunol.* 2004;4:159–163.
14. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(suppl 1):S2–S8.
15. Abelson MB, Welch DL. An evaluation of onset and duration of action of patanol (olopatadine hydrochloride ophthalmic solution 0.1%) compared to Claritin (loratadine 10 mg) tablets in acute allergic conjunctivitis in the conjunctival allergen challenge model. *Acta Ophthalmol Scand Suppl.* 2000;230:60–63.
16. Abelson MB, Kaplan AP. A randomized, double-blind, placebo-controlled comparison of emedastine 0.05% ophthalmic solution with loratadine 10 mg and their combination in the human conjunctival allergen challenge model. *Clin Ther.* 2002;24:445–456.
17. Kato M, Nishida A, Aga Y. Pharmacokinetic and pharmacodynamic evaluation of the central effect of the novel antiallergic agent bepotastine besilate. *Arzneimittelforschung.* 1997;47:1116–1124.
18. Baba S, Takasaka T, Baba K, et al. Long-term treatment of TAU-284 (betotastine besilate) on perennial allergic rhinitis [in Japanese]. *J Clin Ther Med.* 1997;13:1361–82.
19. Ishibashi Y, Harada S, Niimura M, et al. Long-term treatment of TAU-284 (betotastine besilate) on chronic urticaria [in Japanese]. *J Clin Ther Med.* 1997;13:1337–1359.
20. Yato N, Murata T, Saito N. Anti-allergic activity of betotastine besilate (TAU-284), a new anti-allergic drug [in Japanese]. *Nippon Yakurigaku Zasshi.* 1997;110:19–29.
21. Sakai A, Kikuchi M, Yato N, Kikkawa H, Saito N, Narita H. Inhibitory effect of betotastine besilate on antigen-induced airway eosinophil infiltration and peripheral blood eosinophilia in mice. *Arzneimittelforschung.* 1997;47:954–958.
22. Ueno M, Inagaki N, Nagai H, Koda A. Antiallergic action of betotastine besilate (TAU-284) in animal models: a comparison with ketotifen. *Pharmacology.* 1998;57:206–214.
23. Ohashi Y. Immunological study of a second-generation antihistamine: the effects of bepotastine besilate on cytokine production from the peripheral blood mononuclear cells in cedar pollen allergy patients [in Japanese]. *Prog Med.* 2004;24:157–159.
24. Kaminuma O, Ogawa K, Kikkawa H, Kikuchi M, Naito K, Ikezawa K. A novel anti-allergic drug, betotastine besilate, suppresses interleukin-5 production by human peripheral blood mononuclear cells. *Biol Pharm Bull.* 1998;21:411–413.
25. Talion [package insert]. Osaka, Japan: Tanabe Seiyaku Co Ltd; 2008.
26. Baba S. Post-marketing surveillance study of Talion® tablets on pediatric allergic rhinitis [in Japanese]. *Rinsho Igaku.* 2002;18:1371–1387.
27. Ito M, Agaogi K, Shimizu H, et al. A clinical study of anti-allergy drugs in relation to allergic rhinitis [in Japanese]. *Allergol Immunol.* 2003;10:88–97.

-
28. Tanaka T, Miyazaki, Ishikawa K. The usefulness of Talion® in relation to nasal congestion in allergic rhinitis [in Japanese]. *Prog Med*. 2004; 24:2037–2044.
29. Abelson MB, Chambers WA, Smith LM. Conjunctival allergen challenge: a clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol*. 1990;108:84–88.
30. Abelson MB, Loeffler O. Conjunctival allergen challenge: models in the investigation of ocular allergy. *Curr Allergy Asthma Rep*. 2003;3: 363–368.
31. Abelson MB. Comparison of the conjunctival allergen challenge model with the environmental model of allergic conjunctivitis. *Acta Ophthalmol Scand Suppl*. 1999;228:38–42.
32. Rosenwasser LJ, Abelson MB, Gomes PJ, Kennedy K. A comparison of olopatadine 0.2% ophthalmic solution versus fluticasone furoate nasal spray for the treatment of allergic conjunctivitis. *Allergy Asthma Proc*. 2008;29:644–653.
33. Crampton HJ. A comparison of the relative clinical efficacy of a single dose of ketotifen fumarate 0.025% ophthalmic solution versus placebo in inhibiting the signs and symptoms of allergic rhinoconjunctivitis as induced by the conjunctival allergen challenge model. *Clin Ther*. 2002; 24:1800–1808.
34. Abelson MB, Gomes PJ, Vogelsson CT, et al. Effects of a new formulation of olopatadine ophthalmic solution on nasal symptoms relative to placebo in two studies involving subjects with allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin*. 2005;21:683–691.
35. Abelson MB. Evaluation of olopatadine, a new ophthalmic antiallergic agent with dual activity, using the conjunctival allergen challenge model. *Ann Allergy Asthma Immunol*. 1998;81:211–218.
36. Abelson MB, Chapin MJ, Kapik BM, Shams NB. Efficacy of ketotifen fumarate 0.025% ophthalmic solution compared with placebo in the conjunctival allergen challenge model. *Arch Ophthalmol*. 2003;121: 626–630.
37. Abelson MB, Gomes P, Crampton HJ, Schiffman RM, Bradford RR, Whitcup SM. Efficacy and tolerability of ophthalmic epinastine assessed using the conjunctival antigen challenge model in patients with a history of allergic conjunctivitis. *Clin Ther*. 2004;26:35–47.
38. Abelson MB, Turner D. A randomized, double-blind, parallel-group comparison of olopatadine 0.1% ophthalmic solution versus placebo for controlling the signs and symptoms of seasonal allergic conjunctivitis and rhinoconjunctivitis. *Clin Ther*. 2003;25:931–947.
39. Abelson MB, Torkildsen GL, Williams JI, et al. 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;31:1908–1921.
40. Abelson MB, Spitalny L. Combined analysis of two studies using the conjunctival allergen challenge model to evaluate olopatadine hydrochloride, a new ophthalmic antiallergic agent with dual activity. *Am J Ophthalmol*. 1998;125:797–804.
41. Moore DS, McCabe GP. Comparing two proportions. In: *Introduction to the Practice of Statistics*. New York, NY: WH Freeman & Co; 1993: 590–596.
42. Berger W, Hampel F, Bernstein J, et al. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2006;97:375–381.
43. Ukai K, Takeuchi M, Masuda S. Clinical pharmacological study of antiallergic agent TAU-184 (bepotastine besilate): the effect on counting of eosinophils in nasal discharge, and the patency improvement of nasal cavity [in Japanese]. *J Clin Ther Med*. 1997;13:1401–1412.
44. Hashiguchi K, Tang H, Fujita T, et al. Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO Chamber). *Expert Opin Pharmacother*. 2009;10:523–529.
45. Ousler GW, Wilcox KA, Gupta G, Abelson MB. An evaluation of the ocular drying effects of 2 systemic antihistamines: loratadine and cetirizine hydrochloride. *Ann Allergy Asthma Immunol*. 2004;93:460–464.
46. Welch D, Ousler GW III, Nally LA, Abelson MB, Wilcox KA. Ocular drying associated with oral antihistamines (loratadine) in the normal population: an evaluation of exaggerated dose effect. *Adv Exp Med Biol*. 2002;506:1051–1055.
- Requests for reprints should be addressed to:*
Jon I. Williams, PhD
ISTA Pharmaceuticals Inc
15295 Alton Pkwy
Irvine, CA 92618
E-mail: jwilliams@istavision.com
-