Pataday® (Olopatadine Hydrochloride Ophthalmic Solution)

Clinical Science Compendium

Summary of peer-reviewed clinical research

Medical Affairs North America

Alcon

INTRODUCTION

At Alcon, our ocular health products for dry eye and ocular allergy, such as olopatadine hydrochloride ophthalmic solution, are designed, manufactured and marketed with a body of science developed through rigorous bench research and clinical studies. As the body of knowledge behind Alcon's products grows, so does the challenge of making our customers aware of its depth. Our medical affairs organization is thus focused on both high-quality data generation and its communication to the clinical community.

High-quality scientific publications are essential to convey the clinical community's knowledge and experience. This clinical science compendium provides a consolidated view of peer-reviewed publications for olopatadine hydrochloride, which is a dual-action agent (antihistamine/mast cell stabilizer) that temporarily relieves itchy eyes due to pollen, ragweed, grass, animal dander and hair. This compendium primarily focuses on the 0.1% solution (Pataday® Twice Daily Relief, formerly prescription Patanol®), the 0.2% solution (Pataday® Once Daily Relief, formerly prescription Pataday®), and the 0.7% solution (Pataday® Once Daily Relief Extra Strength, formerly prescription PAZEO®).

In addition to exploring this compendium, we encourage you to visit Alcon's Medical Affairs website—AlconScience.com—to learn more about how medical science matters to us. Beyond scientific publications relating to Alcon's portfolio, you will find more information on independent medical educational grants, teaching facility equipment placement, and areas of interest for investigator-initiated trials.

METHODOLOGY

The 32 articles summarized in this compendium were identified using the PubMed and Google Scholar databases incorporating the search terms "olopatadine," "Pataday," "Pazeo" and "Patanol." Articles were included when they were published between January 1, 1998 and December 31, 2019 and contained research relevant to olopatadine hydrochloride ophthalmic solution 0.1%, 0.2%, and 0.7% (PAZEO®), for the treatment of itching or redness in the eyes due to allergies. Only manuscripts published in peer-reviewed journals and available in English were included in this compendium.

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Abelson MB. *Ann Allergy Asthma Immunol.* 1998;81:211-218

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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. 4
Abelson MB, Welch DL. *Acta Ophthalmol Scand Suppl.* 2000;(230):60-63.

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Artal MN, Luna JD, Discepola M. *Acta Ophthalmol Scand Suppl.* 2000;(230):64-65.

A Comparison of the Relative Efficacy and Clinical Performance of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Ketotifen Fumarate 0.025% Ophthalmic Solution in the Conjunctival Antigen Challenge Model. 6
Berdy GJ, Spangler DL, Bensch G, Berdy SS, Brusatti RC. *Clin Ther.* 2000;22:826-833.

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Spangler DL, Bensch G, Berdy GJ. *Clin Ther.* 2001;23:1272-1280.

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Katelaris CH, Ciprandi G, Missotten L, Turner FD, Bertin D, Berdeaux G; International Olopatadine Study Group. *Clin Ther.* 2002;24:1561-1575.

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Leonardi A, Abelson MB. *Clin Ther.* 2003;25:2539-2552.

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Yaylali V, Demirlenk I, Tatlipinar S, Ozbay D, Esme A, Yildirim C, Ozden S. *Acta Ophthalmol Scand.* 2003;81:378-382.

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Double-Masked, Randomized, Parallel-Group Study Comparing Olopatadine 0.1% Ophthalmic Solution with Cromolyn Sodium 2% and Levocabastine 0.05% Ophthalmic Preparations in Children with Seasonal Allergic Conjunctivitis. 14
Ciprandi G, Turner D, Gross RD. *Curr Ther Res Clin Exp.* 2004;65:186-199.

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Efficacy and Response with Olopatadine Versus Epinastine in Ocular Allergic Symptoms: A Post Hoc Analysis of Data from a Conjunctival Allergen Challenge Study. 16
Finegold I, Granet DB, D'Arienzo PA, Epstein AB. *Clin Ther.* 2006;28:1630-1638.

Comparison of the Efficacy of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Artificial Tears in Seasonal Allergic Conjunctivitis. 17
Kamis U, Ozturk BT, Ozkagnici A, Gunduz K. *Acta Ophthalmol Scand.* 2006;84:148-149.

Efficacy of Olopatadine HCl 0.1%, Ketotifen Fumarate 0.025%, Epinastine HCl 0.05%, Emedastine 0.05% and Fluorometholone Acetate 0.1% Ophthalmic Solutions for Seasonal Allergic Conjunctivitis: A Placebo-Controlled Environmental Trial. 18
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Fujishima H, Ohashi Y, Takamura E. *Ann Allergy Asthma Immunol.* 2014;113:476-481.

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Dudeja L, Janakiraman A, Dudeja I, Sane K, Babu M. *Indian J Ophthalmol.* 2019;67:1400-1404.

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Efficacy of Olopatadine Ophthalmic Solution 0.2% in Reducing Signs and Symptoms of Allergic Conjunctivitis. 24
Abelson MB, Gomes PJ, Pasquine T, Edwards MR, Gross RD, Robertson SM. *Allergy Asthma Proc.* 2007;28:427-433.

Safety and Tolerability of Olopatadine 0.2% in Children and Adolescents. 25
Lichtenstein SJ, Pasquine TA, Edwards MR, Wells DT, Gross RD, Robertson SM. *J Ocul Pharmacol Ther.* 2007;23:366-371.

A Comparison of Olopatadine 0.2% Ophthalmic Solution Versus Fluticasone Furoate Nasal Spray for the Treatment of Allergic Conjunctivitis. 26
Rosenwasser LJ, Mahr T, Abelson MB, Gomes PJ, Kennedy K. *Allergy Asthma Proc.* 2008;29:644-653.

A Multicenter Evaluation of the Efficacy and Duration of Action of Alcaftadine 0.25% and Olopatadine 0.2% in the Conjunctival Allergen Challenge Model. 27
Ackerman S, D'Ambrosio F Jr, Greiner JV, Villanueva L, Ciolino JB, Hollander DA. *J Asthma Allergy.* 2013;6:43-52.

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Torkildsen G, Narvekar A, Bergmann M. *Clin Ophthalmol.* 2015;9:1703-1713.

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Meier E, Narvekar A, Iyer GR, DuBiner HB, Vutikullird A, Wirta D, Sall K. *Clin Ophthalmol.* 2017;11:669-681.

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Fidler ML, Ogundele A, Covert D, Sarangapani R. *J Pharmacokinet Pharmacodyn.* 2018;45:593-605.

Combined Analysis of Two Studies Using the Conjunctival Allergen Challenge Model to Evaluate Olopatadine Hydrochloride, a New Ophthalmic Antiallergic Agent with Dual Activity

Signs and Symptoms

Adverse Events

Abelson et al. *Am J Ophthalmol.* 1998;125:797-804

OVERVIEW

STUDY DESIGN
Two double-masked, randomized, placebo-controlled, contralateral eye comparison studies using the conjunctival allergen challenge model

STUDY PURPOSE
To evaluate the effectiveness and safety of olopatadine hydrochloride and to determine its optimal concentration and the onset and duration of action for treating allergic conjunctivitis

STUDY SITE(S)
United States

PATIENTS
One hundred sixty-nine (169) healthy subjects with a history of active allergic conjunctivitis within the previous two seasons but not receiving current treatment

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.05% and 0.1% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Itching and redness for both eyes at 3, 10, and 20 minutes after the conjunctival allergen challenge

ANALYSIS AND CONCLUSIONS

The combined results of these two studies indicate that olopatadine is an effective ocular antiallergic agent with a rapid onset and prolonged duration of action with excellent tolerability.

Olopatadine 0.1% was well-tolerated by all subjects.

STUDY RESULTS#

SIGNS AND SYMPTOMS

- Olopatadine 0.1% was significantly more effective than placebo in inhibiting signs of allergic conjunctivitis when administered either 27 minutes or 8 hours before conjunctival allergen challenge
- The mean itching and redness (the sum of scores for ciliary, conjunctival, and episcleral redness) scores were significantly ($P<0.05$) lower in olopatadine-treated eyes compared with placebo-treated eyes at all time points (3, 10, and 20 minutes) after the 27-minute and 8-hour challenges **(Table 1)**

ADVERSE EVENTS

- There were no serious adverse events and no ocular or nonocular adverse events (AEs) rated as possibly, probably, or definitely drug-related in either study
- In study 1, three subjects experienced AEs, none related to administration of study drug or placebo
- In study 2, 10/60 subjects (16.7%) in the 0.05% olopatadine treatment group and 9/60 subjects (15%) in the 0.1% olopatadine treatment group experienced AEs, none related to administration of study drug or placebo

#Results for endpoints outside FDA approved indications for use are not included.

Table 1. Mean itching and redness scores for the 8-hour challenge.

		3 minutes	10 minutes	20 minutes	3 minutes	10 minutes	20 minutes
	N	Mean (SD) Itching Scores			Mean (SD) Redness Scores*		
Olopatadine 0.1% SEM	77	0.56† (0.8) 0.09	0.58† (0.8) 0.09	0.47† (0.8) 0.09	2.13† (1.9) 0.21	4.26† (2.1) 0.24	4.52† (2.1) 0.24
Placebo for 0.1% SEM	77	1.81 (0.9) 0.1	1.98 (1) 0.11	1.49 (1.1) 0.12	3.63 (2.1) 0.23	5.67 (1.7) 0.19	5.56 (1.8) 0.21

**Mean redness scores constitute the sum of redness scores (0 to 4) from three vessel beds; therefore, the possible range is 0 to 12. †P=0.0001 for comparison with placebo.*

Evaluation of Olopatadine, a New Ophthalmic Antiallergic Agent with Dual Activity, Using the Conjunctival Allergen Challenge Model

Signs and Symptoms

Adverse Events

Abelson. ***Ann Allergy Asthma Immunol.*** **1998;81:211-218**

OVERVIEW

STUDY DESIGN

Placebo-controlled, randomized, double-masked, parallel-group, single-center study with five outpatient visits at least 7 days apart using the conjunctival allergen challenge model

STUDY PURPOSE

To evaluate efficacy and safety, determine optimal concentration, and demonstrate onset and duration of action of olopatadine

STUDY SITE(S)

United States

PATIENTS

Ninety-eight (98) healthy, allergy-positive subjects with a recent history of active allergic conjunctivitis but not receiving current treatment

STUDY AGENTS

Olopatadine hydrochloride ophthalmic solution 0.01%, 0.05%, 0.1%, and 0.15% (Alcon Vision, LLC)

KEY ENDPOINT(S)

Intensity of itching and redness for both eyes at 3, 10, and 20 minutes after the conjunctival allergen challenge

ANALYSIS AND CONCLUSIONS

Results from this study indicate that olopatadine ophthalmic solution is safe and effective in the treatment of allergic conjunctivitis, with the 0.1% concentration of olopatadine being optimal.

The rapid onset and at least 8 hour duration of action of olopatadine indicate that the drug can be used twice daily.

STUDY RESULTS[#]

ONSET AND DURATION OF ACTION

- When allergen challenge was performed 27 minutes after administration of study drug, olopatadine 0.1% was significantly more effective than placebo in reducing mean itching and redness scores at 3, 10 and 20 minutes post-challenge ($P<0.05$)
- At 6 and 8 hours after study drug instillation:
  - Differences from placebo for mean itching scores ranged from 0.4 to 1.7 and were significantly ($P<0.05$) lower in olopatadine-treated eyes than in placebo treated eyes at all time points for all four concentrations during both the 6-hour and the 8-hour challenges
  - Differences from placebo for mean redness scores ranged from 0.5 to 2.3, which represented a statistically significant reduction of redness at most time points

ADVERSE EVENTS

- During the study, six subjects experienced seven adverse events, none of which were related to admin-istration of study drug and none were considered serious

[#]Results for endpoints outside FDA approved indications for use are not included.

Comparative Evaluation of Olopatadine Ophthalmic Solution (0.1%) Versus Ketorolac Ophthalmic Solution (0.5%) Using the Provocative Antigen Challenge Model

Signs and Symptoms

Patient-Reported Outcomes

Adverse Events

Deschenes et al. *Acta Ophthalmol Scand Suppl.* 1999;(228):47-52

OVERVIEW

STUDY DESIGN
Randomized, double-blind, single-center, crossover study incorporating a provocative antigen challenge model

STUDY PURPOSE
To compare the efficacy and safety of olopatadine hydrochloride ophthalmic solution 0.1% versus ketorolac ophthalmic solution 0.5% in a clinical model of acute allergic conjunctivitis

STUDY SITE(S)
Not specified

PATIENTS
Thirty-six (36) patients; mean age of 36 years, range: 19 to 68 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); ketorolac ophthalmic solution 0.5% (Allergan, Inc.)

KEY ENDPOINT(S)
Itching and hyperemia scores recorded at 3, 10, and 20 minutes post-allergen administration, which occurred 27 minutes after drug application; patient-reported discomfort

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% significantly reduced itching and redness in all vessel beds compared to placebo at all time points assessed following an ocular allergen challenge; ketorolac 0.5% failed to significantly reduce itching or redness at the same time points.

In addition to the better efficacy of olopatadine 0.1% observed in the study, patients treated with this agent reported significantly greater comfort than with ketorolac 0.5%.

STUDY RESULTS

IMPROVEMENT IN SIGNS AND SYMPTOMS

- Olopatadine 0.1% significantly (P<0.0001) reduced both ocular itching (**Figure 1**) and hyperemia in all three vessel beds (conjunctival, ciliary, and episcleral) (**Table 1**) compared to placebo at all time points tested following allergen challenge
- Ketorolac 0.5% did not significantly reduce itching (**Figure 1**) and actually showed an increase in hyperemia compared to placebo (**Table 1**); this increase in hyperemia was statistically significant 10 and 20 minutes following antigen challenge
- Olopatadine 0.1% was significantly more effective than ketorolac 0.5% in reducing hyperemia (P<0.001) (**Table 1**) and ocular itching (P<0.05) at 3, 10 and 20 minutes following antigen challenge

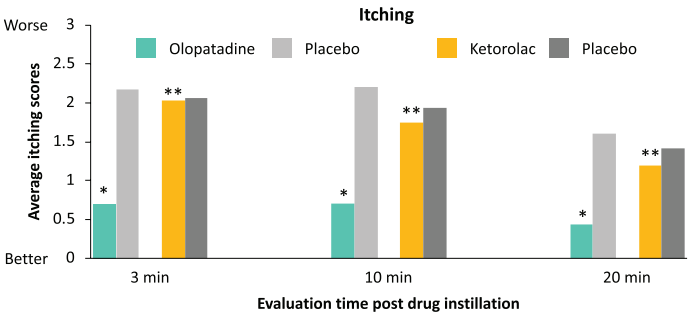
PATIENT-REPORTED DISCOMFORT

- Olopatadine 0.1% was significantly (P<0.05) more comfortable than ketorolac 0.5% as reported by subjects immediately following drug instillation
- Patients treated with olopatadine 0.1% a mean discomfort score of 0.17 (scale of 0 = none, 3 = severe), while patients treated with ketorolac 0.5% patients had a score of 0.50

ADVERSE EVENTS

- No adverse events (AEs) were reported by the 36 patients treated with olopatadine, while AEs were reported in 2/36 patients (5.6%) treated with ketorolac 0.5% (abdominal pain and non-allergic rhinitis, neither associated with study drug)

Figure 1. Average itching scores. Itching was rated by patients on a 0 (none) to 4 (extremely severe) scale.



**Olopatadine was statistically superior to placebo in reducing itching (P<0.001).*
***There were no statistically significant differences between ketorolac 0.5% and placebo (P>0.05).*

Table 1. Mean difference in hyperemia scores in three vessel beds after antigen challenge of study drug compared to placebo and olopatadine 0.1% compared to ketorolac 0.5%.

	Conjunctival time after challenge			Ciliary time after challenge			Episcleral time after challenge		
	3 min	10 min	20 mins	3 min	10 min	20 min	3 min	10 min	20 min
Olopatadine 0.1%	1.14	1.57	1.64	1.16	1.58	1.68	1.43	1.83	1.29
Placebo	2.10	2.47	2.33	2.13	2.64	2.56	2.21	2.56	2.53
Difference	-0.96*	-0.90*	-0.69*	-0.97*	-1.06*	-0.88*	-0.79*	-0.72*	-0.61*
Ketorolac 0.5%	2.10	2.57	2.50	2.24	2.76	2.61	2.30	2.67	2.56
Placebo	1.97	2.38	2.25	2.14	2.50	2.43	2.16	2.44	2.29
Difference	0.13	0.19	0.25	0.10	0.26	0.18	0.14	0.22	0.26
Olopatadine 0.1% - ketorolac 0.5%	-0.99*	-1.00*	-0.86*	-1.13*	-1.18*	-0.93*	-0.91*	-0.83*	-0.64*

**P<0.0001.*

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

Abelson et al. *Acta Ophthalmol Scand Suppl.* 2000;(230):60-63

OVERVIEW

STUDY DESIGN
Randomized, double-masked, single center, contralateral controlled, conjunctival allergen challenge model study

STUDY PURPOSE
To compare the clinical efficacy of localized olopatadine hydrochloride ophthalmic solution 0.1% with systemic loratadine 10 mg tablets in a conjunctival allergen challenge model

STUDY SITE(S)
United States

PATIENTS
Twenty-nine (29) patients: 15 received loratadine 10 mg along with olopatadine 0.1% in one eye and placebo in the contralateral eye; 14 received placebo tablet along with olopatadine 0.1% in one eye and placebo in the contralateral eye

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); loratadine 10 mg (Bayer HealthCare)

KEY ENDPOINT(S)
Onset of action and duration of effect of study agents on ocular itching at one and eight hours after drug administration, respectively

ANALYSIS AND CONCLUSIONS

A statistically significant and clinically relevant difference in itch relief was seen in favor of olopatadine 0.1% compared to loratadine at onset.

Eight hours after drug administration, the difference in ocular itch was not clinically relevant between study drugs.

STUDY RESULTS

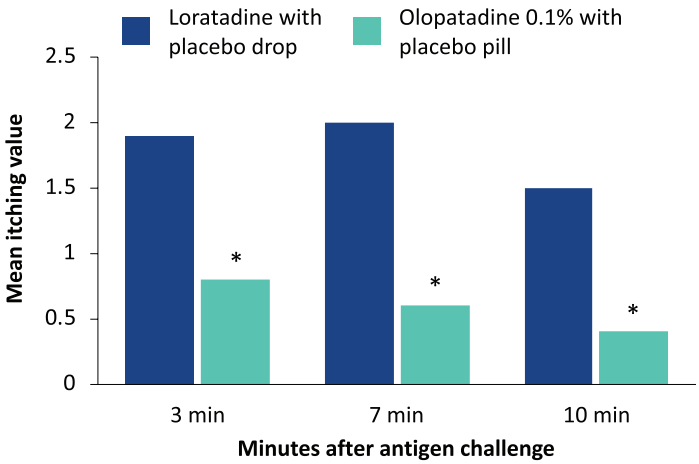
ONSET OF ACTION

- Eyes treated with olopatadine 0.1% (concomitant with placebo tablet) had significantly lower ocular itching scores when compared to eyes treated with placebo drops (concomitant with loratadine) at 3 minutes (P=0.0002), 7 minutes (P=0.0001) and 10 minutes (P=0.0004) in the onset of action evaluation (**Figure 1**)
- Itching results were also clinically relevant (score unit decrease of at least 1) at 3, 7 and 10 minutes, which demonstrates a quicker onset of action. (**Figure 1**)

DURATION OF ACTION

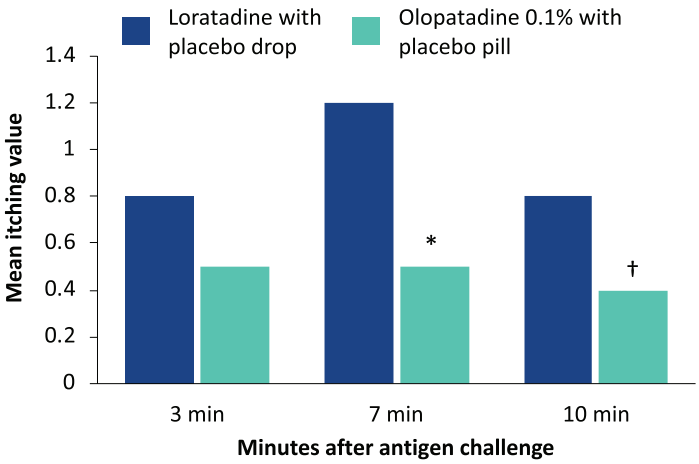
- Eyes treated with olopatadine 0.1% (concomitant with placebo tablet) had significantly lower ocular itching scores at 7 minutes (P= 0.0052) in the duration of action evaluation, and there was a statistical trend at 10 minutes (P=0.0906). Differences were not clinically relevant. (**Figure 2**)

Figure 1. Mean itching values for onset of action evaluation at 3, 7, and 10 minutes post-challenge in eyes treated with loratadine with placebo drops (n=15) and olopatadine ophthalmic solution 0.1% with placebo tablet (n=14).



*Results were statistically significant (*P<0.05) and clinically significant (score unit difference of at least 1 unit) at all time points.*

Figure 2. Mean itching values for duration of action evaluation at 3, 7, and 10 minutes post-challenge in subjects treated with loratadine with placebo drops (n=15) and olopatadine ophthalmic solution 0.1% with placebo tablet (n=14).



[†]P<0.05; results statistically significant at 7 minutes. †0.05<P<0.1; trend toward significance observed at 10 minutes.

A Forced Choice Comfort Study of Olopatadine Hydrochloride 0.1% Versus Ketotifen Fumarate 0.05%

Adverse Events

Patient-Reported Outcomes

Artal et al. *Acta Ophthalmol Scand Suppl.* 2000;(230):64-65

OVERVIEW

STUDY DESIGN
Double-masked, multi-centered, randomized trial

STUDY PURPOSE
To compare the ocular comfort of olopatadine hydrochloride ophthalmic solution 0.1% versus ketotifen fumarate 0.05% based on the "forced choice" of patients

STUDY SITE(S)
Canada

PATIENTS
Eighty (80) patients asked to choose which agent is more comfortable

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); ketotifen fumarate ophthalmic solution 0.05% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Ocular comfort, adverse reactions (collected secondarily at 1 of the 2 study sites)

ANALYSIS AND CONCLUSIONS

All patients in this study chose olopatadine 0.1% as the most comfortable ophthalmic solution option over ketotifen fumarate 0.05%.

Only one patient reported no burning after ketotifen instillation.

STUDY RESULTS

PATIENT-REPORTED DISCOMFORT

- All subjects (100%) selected olopatadine 0.01% as more comfortable than ketotifen fumarate 0.05% (**Figure 1**)

ADVERSE EVENTS

- One study site (n = 35) reported a 49% incidence of moderate burning and a 49% incidence of mild burning after ketotifen fumarate 0.05% instillation; only 1 subject (2% of the population) at this site experienced no burning after ketotifen fumarate 0.05% instillation (**Figure 2**)
- Burning with ketotifen fumarate 0.05% instillation was also noted at the second site, but its exact incidence was not reported
- There were no reports of discomfort associated with olopatadine 0.1% instillation (**Figure 2**)

Figure 1. Percentage of patients (n=80) who preferred olopatadine 0.1% to ketotifen fumarate 0.05%.

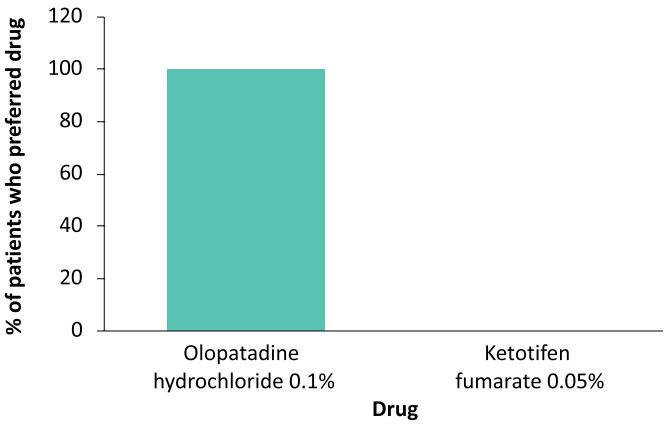
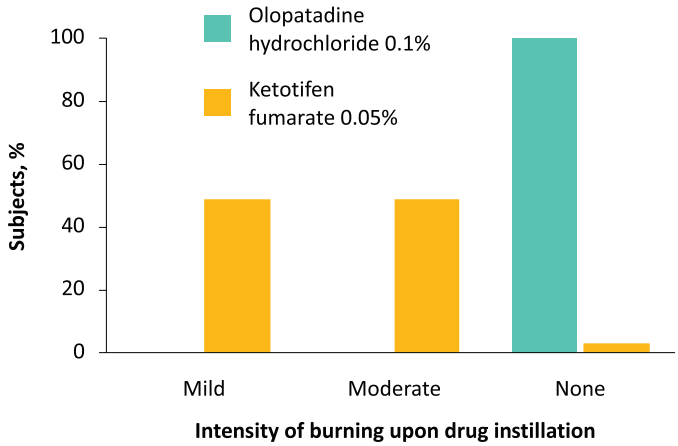


Figure 2. Adverse events (moderate burning, mild burning or no burning) reported after drug instillation; there were no reported adverse events with olopatadine 0.1%.



Signs and Symptoms

Patient-Reported Outcomes

A Comparison of the Relative Efficacy and Clinical Performance of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Ketotifen Fumarate 0.025% Ophthalmic Solution in the Conjunctival Antigen Challenge Model

Berdy et al. *Clin Ther.* 2000;22:826-833

OVERVIEW

STUDY DESIGN

Prospective, randomized, double-masked, contralaterally controlled, single-center, conjunctival antigen challenge study

STUDY PURPOSE

To compare the relative efficacy and clinical performance of olopatadine hydrochloride ophthalmic solution 0.1% and ketotifen fumarate ophthalmic solution 0.025% in the conjunctival antigen challenge model

STUDY SITE(S)

United States

PATIENTS

Thirty-two (32) patients who were previously involved in ocular allergy studies

STUDY AGENTS

Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); ketotifen fumarate ophthalmic solution 0.025% (Alcon Vision, LLC)

KEY ENDPOINT(S)

Comfort immediately following drug instillation; itching at 3, 5, and 10 minutes after the conjunctival allergen challenge; patient-reported treatment preference

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% was more effective than ketotifen 0.025% in reducing the itching associated with allergic conjunctivitis in this antigen challenge model.

Olopatadine 0.1% caused less ocular discomfort than ketotifen 0.025% and was preferred by approximately 3 times as many patients as was ketotifen.

STUDY RESULTS

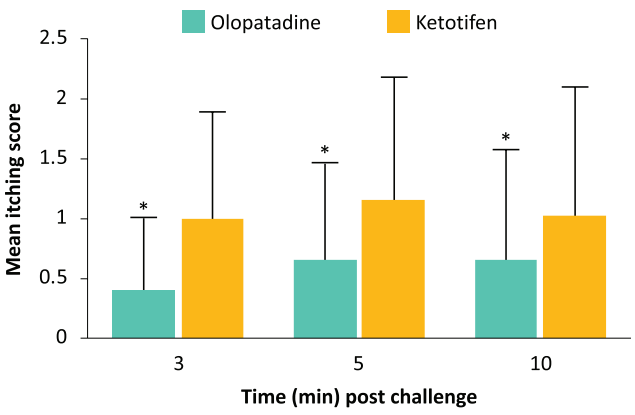
EFFICACY OUTCOMES

- Olopatadine 0.1% was significantly more effective than ketotifen 0.025% at all time points (3, 5, and 10 minutes) in reducing the itching induced by the conjunctival antigen challenge ($P<0.05$) (**Figure 1**)
- Mean efficacy scores for olopatadine 0.1% were significantly higher than those for ketotifen 0.025% at 3 and 5 minutes postchallenge (1.84 and 1.75 vs 1.25 and 1.34; $P<0.05$) (**Figure 2**)

COMFORT AND PATIENT PREFERENCE

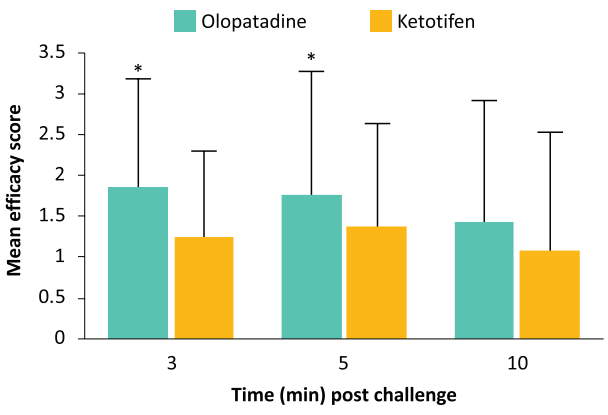
- Olopatadine 0.1%-treated eyes were rated significantly more comfortable than those treated with ketotifen 0.025% immediately after drug instillation (1.25 vs 2.09; $P < 0.05$) and 12 hours later, as measured by patient ratings of ocular comfort (scale of 0 to 8, where 8 is least comfortable)
- Of the 22 subjects who had a preference, 16 (73%) identified olopatadine 0.1% and 6 (27%) identified ketotifen 0.025% as the more tolerable agent immediately after administration (and before the antigen challenge)
- At the end of the study, 16/22 (73%) patients with a preference reported being more satisfied with olopatadine 0.1% than with ketotifen 0.025% based on comfort and efficacy

Figure 1. Mean itching scores for olopatadine 0.1% and ketotifen 0.025% at 3, 5 and 10 minutes post-challenge (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = unusually severe). Challenge was conducted 12 hours after drug instillation.



**P<0.05 vs ketotifen 0.025%.*

Figure 2. Mean efficacy scores for olopatadine 0.1% and ketotifen 0.025% at 3, 5 and 10 minutes post-challenge. Efficacy score is defined as the difference between the mean itching score at visit 2 (untreated baseline) and the mean itching score at visit 3 (after drug treatment).



**P<0.05 vs ketotifen 0.025%.*

Comparison of the Clinical Efficacy and Comfort of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Nedocromil Sodium 2% Ophthalmic Solution in the Human Conjunctival Allergen Challenge Model

Signs and Symptoms

Patient-Reported Outcomes

Butrus et al. *Clin Ther.* 2000;22:1462-1472

OVERVIEW

STUDY DESIGN
Single center, 3-visit, randomized, double-masked, contralaterally controlled study

STUDY PURPOSE
To compare the clinical efficacy and comfort of olopatadine hydrochloride ophthalmic solution 0.1% with that of nedocromil sodium ophthalmic solution 0.2% in a conjunctival allergen challenge model

STUDY SITE(S)
North America

PATIENTS
Forty-nine (49) patients with a history of allergic conjunctivitis who responded to conjunctival allergen challenge (mean age range across groups 42.0 to 47.5 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); nedocromil sodium ophthalmic solution 0.2% (Allergan plc)

KEY ENDPOINT(S)
Reduction in itching 3, 5 and 10 minutes after challenge; patient assessment of efficacy and comfort at the end of the study

ANALYSIS AND CONCLUSIONS

In the conjunctival allergen challenge model, olopatadine 0.1% was more efficacious and comfortable than nedocromil 0.2% in reducing the itching associated with allergic conjunctivitis.

Olopatadine was clinically and statistically superior to nedocromil at reducing itching, and of the 14 subjects treated with olopatadine and nedocromil who stated a preference, 10 (71%) were more satisfied with olopatadine than with nedocromil.

STUDY RESULTS

OCULAR ITCHING

- Olopatadine 0.1% was clinically and statistically superior to nedocromil 0.2% at reducing itching in the conjunctival allergen challenge model (mean unit difference: -1.60 at 3 minutes, -1.68 at 5 minutes, -1.19 at 10 minutes; P<0.001) (**Table 1**)
- Olopatadine 0.1%-treated eyes (n=40) had itching scores >2 units lower than eyes receiving placebo (n=22), a clinically and statistically significant difference (P<0.001)
- The comparison between nedocromil 0.2%-treated eyes (n=36) and eyes receiving placebo (n=22) exhibited a much smaller treatment effect than did the olopatadine 0.1%-placebo comparison
- No clinically significant differences were observed between eyes receiving nedocromil 0.2% and placebo; however, a statistically significant difference in favor of nedocromil 0.2% in relief of itching was seen at 3 minutes (P=0.045)

PATIENT-REPORTED OUTCOMES

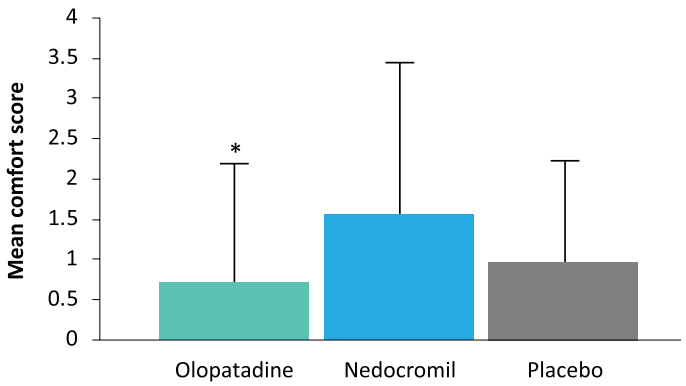
- Olopatadine 0.1%-treated eyes were rated as being significantly more comfortable than nedocromil sodium 0.2%-treated eyes (0.73 vs 1.55; P=0.034) (**Figure 1**)
- Of the 14 subjects treated with olopatadine 0.1% and nedocromil 0.2% who stated a preference, 10 (71%) were more satisfied with olopatadine 0.1% than with nedocromil 0.2%

Table 1. Mean difference between scores for itching 3, 5, and 10 minutes after conjunctival allergen challenge.

Time after challenge (minutes)	Olopatadine 0.1% vs placebo	Nedocromil 0.2% vs placebo	Olopatadine 0.1% vs nedocromil 0.2%
	Mean difference (SD)		
3	-2.16*† (0.98)	-0.56* (0.95)	-1.60‡ (0.82)
5	-2.15*† (1.04)	-0.37 (1.00)	-1.68‡ (0.92)
10	-1.59*† (1.05)	-0.40 (1.11)	-1.19‡ (1.08)

*P<0.05 vs placebo
†Clinically significant (>1 unit difference in itching) vs placebo.
‡Both statistically significant (P<0.05) and clinically significant (>1 unit difference in itching) vs nedocromil 0.2%

Figure 1. Mean comfort scores (8-point scale, from 0 = more comfort to 8 = less comfort) immediately after instillation of olopatadine 0.1%, nedocromil 0.2%, or placebo.



*P=0.034 versus nedocromil 0.2%.

Evaluation of the Efficacy of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Azelastine Hydrochloride 0.05% Ophthalmic Solution in the Conjunctival Allergen Challenge Model

Spangler et al. *Clin Ther.* 2001;23:1272-1280

OVERVIEW

STUDY DESIGN
Prospective, randomized, double-masked, contralaterally controlled, multicenter, allergen-challenge study

STUDY PURPOSE
To compare the efficacy of olopatadine hydrochloride ophthalmic solution 0.1% versus azelastine hydrochloride ophthalmic solution 0.05% and placebo (artificial tears) in the conjunctival allergen challenge model

STUDY SITE(S)
United States

PATIENTS
One-hundred and eleven (111) patients with a history of allergic conjunctivitis who responded to conjunctival allergen challenge (mean age range across groups 37.3 to 41.2 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); azelastine hydrochloride ophthalmic solution 0.05% (MedPointe Pharmaceuticals)

KEY ENDPOINT(S)
Itching assessments immediately after challenge every 30 seconds for 20 minutes

ANALYSIS AND CONCLUSIONS

In this study, olopatadine 0.1% was significantly more effective than azelastine 0.05% in the management of itching associated with allergic conjunctivitis in the conjunctival allergen challenge model.

The authors noted that olopatadine has been shown to have mast-cell stabilization properties in studies of human conjunctival mast cells.

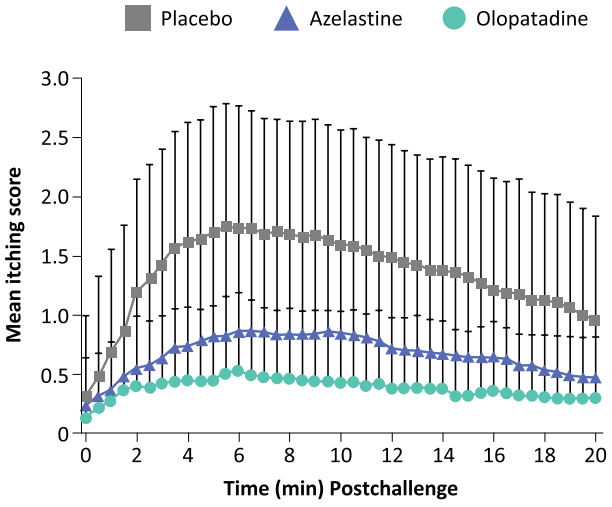
STUDY RESULTS

OCULAR ITCHING

- At the baseline challenge before treatment was initiated, there were no statistically significant differences in mean itching scores among the eyes assigned to olopatadine 0.1%, azelastine 0.05% or placebo groups
- After initiation of treatment, peak mean itching scores were delayed (occurring 2.5 minutes later) for all treated eyes compared with the baseline challenge (**Figure 1**)
- The magnitude of itching also decreased for placebo eyes compared with baseline (**Figure 1**); possible explanations include the occurrence of mast cell fatigue after 3 successive allergen challenges within 3 weeks or the diluent effect of the placebo
- Overall, olopatadine 0.1% was significantly more effective than azelastine 0.05% in reduction of itching post challenge (P<0.05); the average mean unit score difference between olopatadine 0.1% and azelastine 0.05% over all time points was -0.28 (**Figure 1**)
- Clinically significant (>1 unit) differences were observed between olopatadine 0.1% and placebo from 3 to 15 minutes after the allergen challenge (average mean unit difference: -0.96 over all time points) (**Figure 1**)
- Azelastine 0.05% was shown to be statistically significantly more effective than placebo (average mean unit difference: -0.68; P<0.05); however, there were no clinically significant differences between azelastine 0.05% and placebo at any time point (**Figure 1**)

Figure 1. Mean itching scores after conjunctival allergen challenge in eyes pretreated with olopatadine 0.1%, azelastine 0.05%, or placebo. Study medication was instilled 5 minutes before challenge. Scale: 0 = no itching to 4 = severe itching.

**P<0.05 versus azelastine 0.05% from 3.5 minutes to 20 minutes.*



Comparison of the Clinical Efficacy and Tolerability of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Loteprednol Etabonate 0.2% Ophthalmic Suspension in the Conjunctival Allergen Challenge Model

Signs and Symptoms

Adverse Events

Berdy et al. *Clin Ther.* 2002;24:918-929

OVERVIEW

STUDY DESIGN
Single-center, randomized, double-masked, parallel-controlled antigen challenge study

STUDY PURPOSE
To compare the efficacy and tolerability of olopatadine hydrochloride ophthalmic solution 0.1%, loteprednol etabonate ophthalmic suspension 0.2%, and placebo in inhibiting early-phase allergic reaction after conjunctival allergen challenge

STUDY SITE(S)
Not specified

PATIENTS
Fifty (50) subjects with a history of seasonal or panseasonal allergic conjunctivitis, but no severe atopic, vernal, or giant papillary conjunctivitis (age range: 21 to 71 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); loteprednol etabonate ophthalmic suspension 0.2% (Bausch + Lomb)

KEY ENDPOINT(S)
Itching at 3, 5, and 10 minutes after challenge; redness at 10, 15, and 20 minutes after challenge, intraocular pressure (IOP) after a 14-day loading period

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% was more efficacious than loteprednol 0.2% in reducing the acute signs and symptoms of seasonal allergic conjunctivitis during the early phase of the ocular allergic reaction and appeared to be better tolerated.

The difference in inhibition of itching and redness was clinically significant and statistically significant in favor of olopatadine compared to loteprednol (15 minutes after drug administration).

STUDY RESULTS

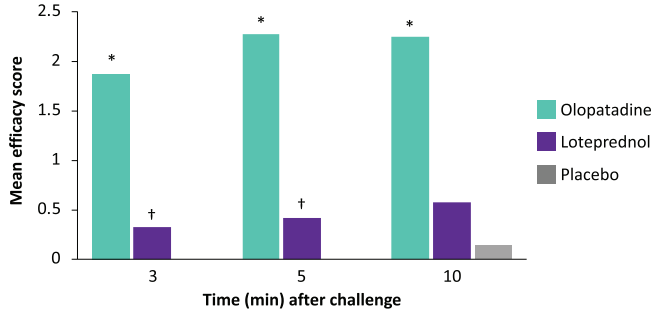
SIGNS AND SYMPTOMS

- Because loteprednol 0.2% requires a loading period to achieve maximum efficacy, subjects assigned this treatment initially received it once daily for 14 days, while olopatadine 0.1% subjects received placebo
- Relief from itching was significantly greater with olopatadine 0.1% than with loteprednol 0.2% (mean itching efficacy score at 3 minutes: 1.875 vs 0.388, respectively; P=0.001; 5 minutes: 2.275 vs 0.425; P<0.001; 10 minutes: 2.263 vs 0.588; P<0.001) (**Figure 1**)
- Olopatadine was also significantly superior to placebo (mean itching efficacy score at 3 minutes: 1.875 vs 0.100; 5 minutes: 2.275 vs 0.000; 10 minutes: 2.263 vs 0.150; all P<0.001) (**Figure 1**)
- For the treatment of redness, olopatadine 0.1% was significantly superior to loteprednol 0.2% (mean redness efficacy score, 10 minutes: 1.300 vs 0.638, respectively; P=0.003; 15 minutes: 1.075 vs 0.525; P=0.011; 20 minutes: 1.000 vs 0.200; P=0.034) (**Figure 2**)
- Olopatadine was also significantly superior to placebo (mean redness efficacy score, 10 minutes: 1.300 vs 0.400; P<0.001; 15 minutes: 1.075 vs 0.425; P=0.012; 20 minutes: 1.000 vs 0.550; P=0.027); no significant difference in redness was seen between loteprednol and placebo at any time point (**Figure 2**)

TOLERABILITY ASSESSEMENT

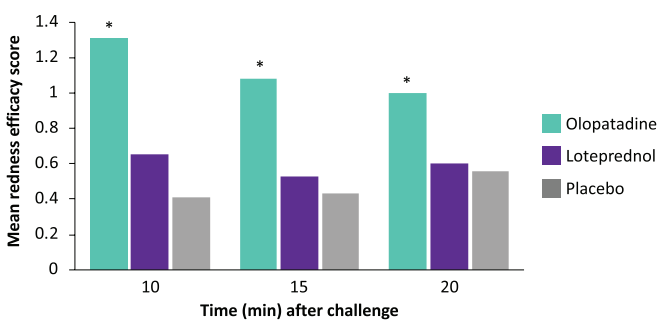
- The loteprednol 0.2% group had a statistically significant increase in IOP after 2 weeks of treatment (P<0.001); no significant changes in IOP were observed in either the olopatadine 0.1% or placebo groups
- No adverse events were reported in the course of the study; subjects reported no ocular stinging, burning, or increased redness with instillation of any of the study medications

Figure 1. Mean itching efficacy scores (calculated as change in itching scores from randomization [visit 2] to treatment evaluation 2 weeks later [visit 3], with greater change indicating greater efficacy) at 3, 5, and 10 minutes after allergen challenge.



**Clinically significant (21 unit difference) and statistically significant (P<0.05) versus loteprednol 0.2% and placebo.*
†P<0.05 versus placebo.

Figure 2. Mean redness efficacy scores (calculated as change in itching scores from randomization [visit 2] to treatment evaluation 2 weeks later [visit 3], with greater change indicating greater efficacy) at 10, 15, and 20 minutes after allergen challenge.



**P<0.05 vs loteprednol 0.2% and placebo.*

A Comparison of the Efficacy and Tolerability of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Cromolyn Sodium 2% Ophthalmic Solution in Seasonal Allergic Conjunctivitis

Katelaris et al. *Clin Ther.* 2002;24:1561-1575

OVERVIEW

STUDY DESIGN
Multicenter, randomized, double-masked, parallel-group trial

STUDY PURPOSE
To compare the efficacy and tolerability of olopatadine hydrochloride ophthalmic solution 0.1% and cromolyn sodium ophthalmic solution 2% in controlling the ocular signs and symptoms of seasonal allergic conjunctivitis

STUDY SITE(S)
Europe and Australia

PATIENTS
One hundred eighty-five (185) patients with a history of allergic conjunctivitis for at least one allergy season; mean age of 35.0 years (age range: 4 to 77 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); cromolyn sodium ophthalmic solution 2%

KEY ENDPOINT(S)
Ocular itching and conjunctival redness at each visit up to day 42 (end of study)

ANALYSIS AND CONCLUSIONS

Over a treatment period of 6 weeks, olopatadine 0.1% twice daily had a significantly greater effect on the ocular signs and symptoms of allergic conjunctivitis than did cromolyn 2% once daily.

Both treatments were well tolerated by patients in all age groups; however, olopatadine 0.1% appeared to have better local tolerability in children less than 11 years of age.

STUDY RESULTS

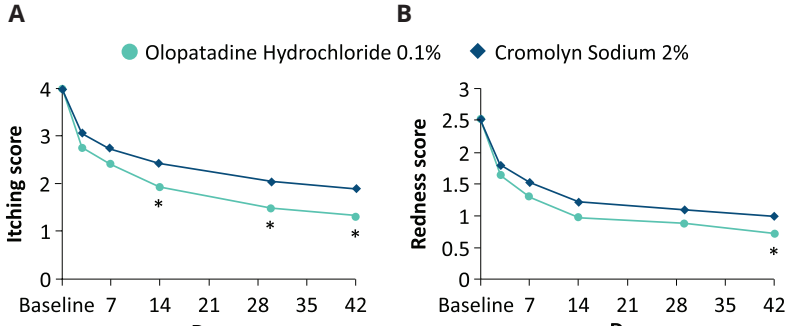
SIGNS AND SYMPTOMS

- After the first instillations of olopatadine 0.1% and cromolyn 2%, self-rated ocular itching and redness decreased rapidly; the effects were statistically significant (P<0.05)
- Thirty minutes after instillation, itching and redness decreased by ~30% and ~20%, respectively, in both groups
- Four hours after instillation, itching had decreased by ~38% in both groups, while redness decreased by ~38% in olopatadine 0.1% patients and ~26% in cromolyn 2% patients
- From days 14 through 42, olopatadine 0.1% was statistically superior to cromolyn 2% in reducing itching (P<0.05), and on day 42 it was statistically superior in reducing redness (P<0.05) (**Figure 1**)
- The difference in physicians' impression of overall improvement on days 30 and 42 significantly favored olopatadine 0.1% over cromolyn 2% (both days, P<0.05)
- Regression slopes correlating itching and redness with pollen count were 5 times lower for olopatadine 0.1% compared with cromolyn 2% (P=0.002 and P=0.016, respectively), indicating that the efficacy of olopatadine 0.1% increased as the pollen count increased (**Figure 2**)

ADVERSE EVENTS

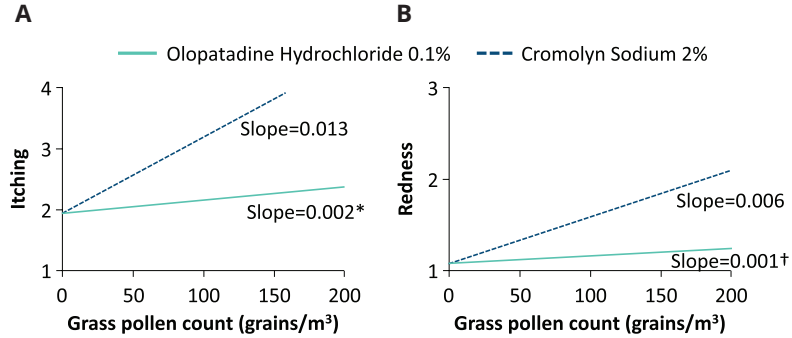
- Four patients in the olopatadine 0.1% group experienced 4 treatment-related ocular adverse events (AEs) of ocular discharge, stinging, and blurred vision; systemic AEs judged related to treatment were dry nose and taste perversion in 2 patients
- Five patients in the cromolyn 2% group experienced 6 treatment-related ocular AEs of dry eye, stinging, pruritus, and lacrimation

Figure 1. Mean (**A**) itching and (**B**) redness scores (per-protocol data set).



**P<0.05.*

Figure 2. Correlation between grass pollen count and symptoms of (**A**) itching and (**B**) redness.



**Slope difference, P = 0.002; †slope difference, P = 0.016.*

Double-Masked, Randomized, Placebo-Controlled Clinical Study of the Mast Cell-Stabilizing Effects of Treatment with Olopatadine in the Conjunctival Allergen Challenge Model in Human

Leonardi et al. *Clin Ther.* 2003;25:2539-2552

OVERVIEW

STUDY DESIGN
Double-masked, randomized, placebo-controlled clinical trial using the conjunctival allergen challenge model

STUDY PURPOSE
To assess the effects of olopatadine hydrochloride ophthalmic solution on the release of mast cell-derived mediators after conjunctival allergen challenge in humans

STUDY SITE(S)
Not specified

PATIENTS
Ten (10) patients with a clinical history of seasonal allergic conjunctivitis (but no current symptoms or treatment at baseline); mean age of 31.5 years (range: 20 to 50 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Itching and redness, inflammatory cell counts (ie, neutrophils, eosinophils, and lymphocytes), histamine levels, intercellular adhesion molecule (ICAM)-1 expression

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% significantly reduced the levels of histamine, cellular infiltrate, and ICAM-1 expression compared with placebo after conjunctival allergen challenge, suggesting that it reduced the release of mast cell-derived mediators in humans.

The inhibition of mediator release correlated with reduction of itching and redness.

STUDY RESULTS

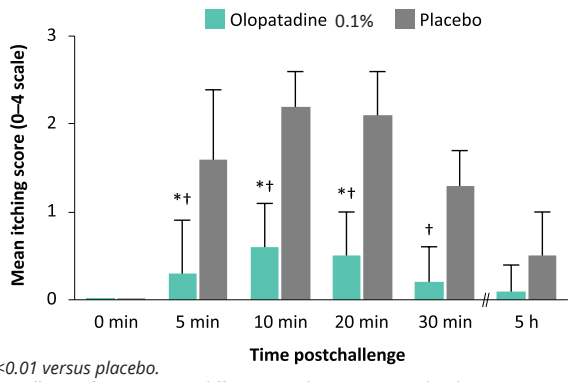
ITCHING AND REDNESS

- Olopatadine 0.1% significantly reduced itching and redness compared with placebo (P<0.01 and P<0.03, respectively) (**Figure 1**)
- Olopatadine 0.1% demonstrated a clinically significant (≥1 unit difference) reduction in redness and itching during the 30-minute post-challenge assessments.

MAST CELL-DERIVED MEDIATORS

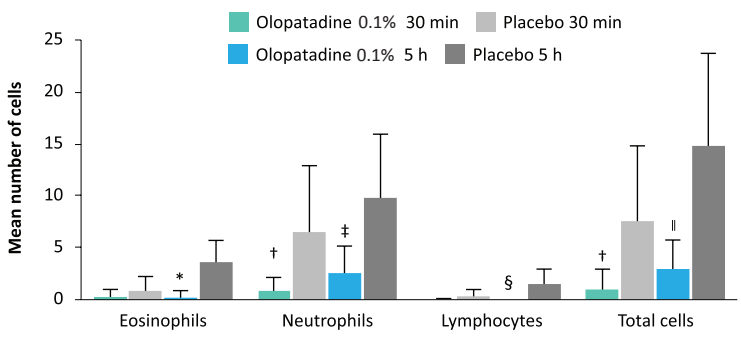
- After the visit 3 (treatment) challenge, olopatadine 0.1% significantly reduced mean (SD) tear histamine levels (7 [8] nM/L) compared with levels measured in the same eyes after the visit 2 (no treatment) challenge (30 [27] nM/L, P = 0.001), whereas placebo did not significantly modify histamine levels (**Figure 2**)
- Comparing histamine levels between the 2 treatments at visit 3, olopatadine 0.1% significantly reduced the levels compared with placebo (7 [8] vs 22 [12] nM/L, P = 0.04)
- Olopatadine 0.1% reduced the number of neutrophils and the total number of cells at 30 minutes (both P=0.015), and the number of eosinophils (P<0.001), neutrophils (P<0.004), lymphocytes (P=0.011), and total number of cells (P=0.001) at 5 hours postchallenge compared with placebo (**Figure 2**)
- Olopatadine 0.1% also significantly reduced ICAM-1 expression compared with placebo at 30 minutes and 5 hours postchallenge (P<0.03 and P<0.01, respectively)

Figure 1. Mean (SD) itching scores on a 0 to 4 scale (0 = none; 4 = severe) in 10 subjects who instilled olopatadine 0.1% or placebo eyedrops twice daily for 5 days before undergoing conjunctival allergen challenge.



**P<0.01 versus placebo.*
†Clinically significant (≥1 unit difference) reduction versus placebo.

Figure 2. Mean (SD) tear cytology at 30 minutes and 5 hours after conjunctival allergen challenge among 10 subjects.



**P<0.001 versus placebo. †P<0.015 versus placebo. ‡P<0.004 versus placebo.*
§P=0.011 versus placebo. ‖P=0.001 versus placebo

Comparative Study of 0.1% Olopatadine Hydrochloride and 0.5% Ketorolac Tromethamine in the Treatment of Seasonal Allergic Conjunctivitis

Yaylali et al. *Acta Ophthalmol Scand.* 2003;81:378-382

OVERVIEW

STUDY DESIGN
Placebo-controlled, randomized, parallel group, single center study

STUDY PURPOSE
To compare the therapeutic effects of two ophthalmic solutions (olopatadine hydrochloride ophthalmic solution 0.1% and ketorolac tromethamine ophthalmic solution 0.5%) with different pharmacological mechanisms on the clinical signs and symptoms of seasonal allergic conjunctivitis

STUDY SITE(S)
Turkey

PATIENTS
Forty (40) patients with signs and symptoms of seasonal allergic conjunctivitis (hyperemia, itching, mucus discharge, tearing); average age 19 years (range: 15 to 25 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); ketorolac tromethamine ophthalmic solution 0.5% (Allergan, Inc.)

KEY ENDPOINT(S)
Principal signs and symptoms of seasonal allergic conjunctivitis (hyperemia and itching) evaluated at 30 minutes and at 2, 7 and 15 days

ANALYSIS AND CONCLUSIONS

Both olopatadine 0.1% and ketorolac 0.5% ophthalmic solutions were found to be effective in alleviating the clinical signs and symptoms of seasonal allergic conjunctivitis compared to placebo.

Olopatadine 0.1% reduced ocular itching significantly more than ketorolac 0.5%, but the difference was not clinically relevant.

STUDY RESULTS

HYPEREMIA AND ITCHING

- Both study parameters (hyperemia and itching) improved significantly in eyes treated with olopatadine 0.1% compared with those receiving placebo at all control examinations (all P<0.05) (**Figures 1,2**)
- Similarly, eyes treated with ketorolac 0.5% showed significant reductions in hyperemia and itching compared with those receiving placebo (all P<0.05) (**Figures 1,2**)
- When the clinical parameters of eyes treated with olopatadine were compared with those treated with ketorolac 0.5%, the mean score of hyperemia was found to be lower in the olopatadine 0.1% group, but the difference was not statistically significant (all P>0.05) (**Figure 2**)
- However, the itching score was significantly lower in the olopatadine 0.1% group than in the ketorolac 0.5% group at day 2 (P=0.018), day 7 (P=0.007) and day 15 (P=0.036) (**Figure 1**)

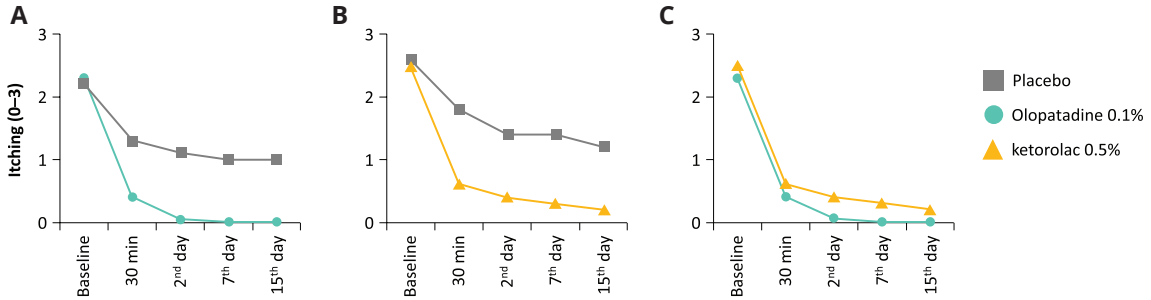


Figure 1. Ocular itching scores. (**A**) Olopatadine 0.1% versus placebo, (**B**) ketorolac 0.5% versus placebo, (**C**) olopatadine 0.1% versus ketorolac 0.5%.

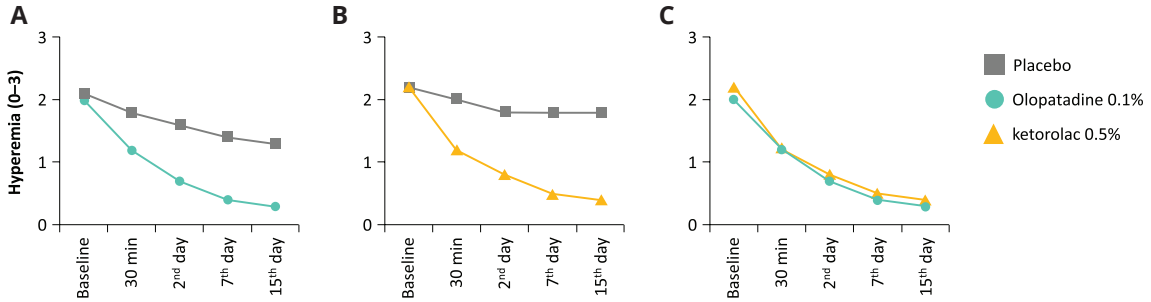


Figure 2. Conjunctival hyperemia scores. (**A**) Olopatadine 0.1% versus placebo, (**B**) ketorolac 0.5% versus placebo, (**C**) olopatadine 0.1% versus ketorolac 0.5%.

Comparative Efficacy of Olopatadine 0.1% Ophthalmic Solution Versus Levocabastine 0.05% Ophthalmic Suspension Using the Conjunctival Allergen Challenge Model

Signs and Symptoms

Patient-Reported Outcomes

Adverse Events

Abelson et al. *Curr Med Res Opin.* 2004;20:1953-1958

OVERVIEW

STUDY DESIGN
Randomized, double-masked, contralateral study using the conjunctival allergen challenge (CAC) model

STUDY PURPOSE
To compare the efficacy of olopatadine hydrochloride ophthalmic solution 0.1% and levocabastine hydrochloride ophthalmic suspension 0.05% in reducing ocular allergic itching and vascular hyperemia (redness) induced by CAC

STUDY SITE(S)
United States

PATIENTS
Sixty-eight (68) patients with a positive allergen skin test and a history of allergic conjunctivitis; mean age of 36.2 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); levocabastine hydrochloride ophthalmic suspension 0.05% (Novartis Ophthalmics)

KEY ENDPOINT(S)
Ocular discomfort after drug instillation; allergic signs (primary: conjunctival, ciliary, and episcleral redness, and sum redness score) and symptoms (primary: itch) at 3 minutes, 10 minutes, and 20 minutes post-challenge; safety analyses

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% was shown at time points within one hour of drug administration to be significantly more effective than levocabastine 0.05% in reducing ocular itching and redness induced by CAC.

Olopatadine 0.1% patients also reported less ocular discomfort after drug instillation.

STUDY RESULTS

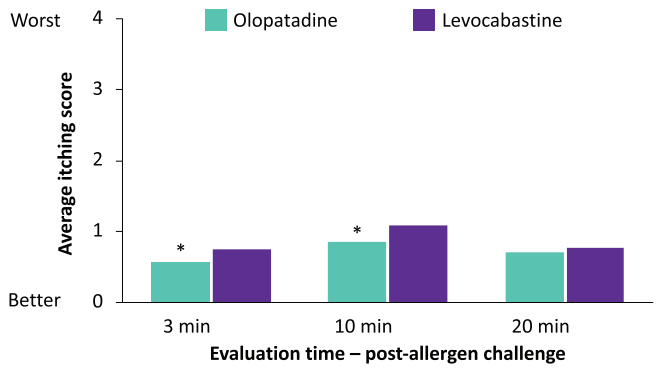
EFFICACY OUTCOMES

- Ocular itching scores for olopatadine 0.1% were significantly lower than for levocabastine 0.05% at 3 and 10 minutes post-challenge (P≤0.001); less itching was observed with olopatadine 0.1% at 20 minutes as well, but this was not statistically significant (**Figure 1**)
- Conjunctival, episcleral and ciliary hyperemia were all significantly less (P≤0.002) in olopatadine 0.1%-treated eyes than in levocabastine 0.05%-treated eyes at 3 (P=0.0001), 10 (P<0.001), and 20 (P<0.0012) minutes post-challenge
- The sum redness score was also significantly less for olopatadine 0.1% at all three time points post-challenge (P<0.0001) (**Figure 2**)

ADVERSE EVENTS

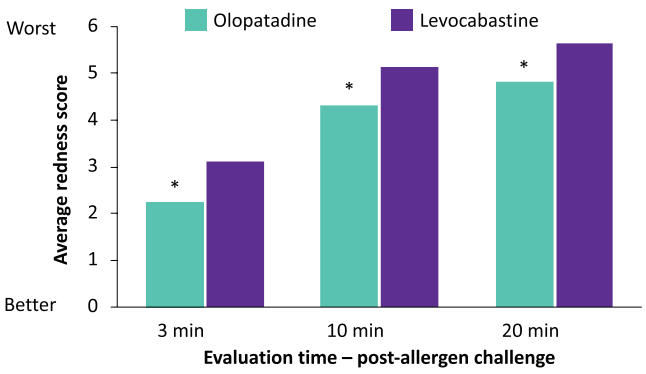
- Adverse events (AEs) related to olopatadine 0.1% and levocabastine 0.05% were mild and easily tolerable; no serious AEs occurred during the study, and no subject was discontinued from the study due to an AE
- Of the 68 subjects exposed to both drugs, one (1.5%) experienced ocular pruritis after drug administration; this was categorized as possibly related to the use of levocabastine 0.05%
- Three subjects (4.41%) reported ocular discomfort in the olopatadine 0.1%-treated eye and 18 (26.5%) in the levocabastine 0.05%-treated eye

Figure 1. Average itching scores for olopatadine 0.1% and levocabastine 0.05% at 3 and 10 minutes after drug instillation. The standardized scale on which subjects rated their ocular itching ranged from 0 (none) to 4 (severe).



*P≤0.001

Figure 2. Average redness scores for olopatadine 0.1% and levocabastine 0.05% at 3, 10 and 20 minutes after drug instillation. The standardized scale on which investigators rated ocular redness ranged from 0 (none) to 4 (extremely severe) for conjunctival, ciliary and episcleral vessel beds. Scores illustrated here are the sum of these three individual redness scores (0–12 range).



*P≤0.0001

Double-Masked, Randomized, Parallel-Group Study Comparing Olopatadine 0.1% Ophthalmic Solution with Cromolyn Sodium 2% and Levocabastine 0.05% Ophthalmic Preparations in Children with Seasonal Allergic Conjunctivitis

Ciprandi et al. *Curr Ther Res Clin Exp.* 2004;65:186-199†

OVERVIEW

STUDY DESIGN
Two double-masked, randomized, parallel-group studies

STUDY PURPOSE
To assess the efficacy and tolerability of olopatadine hydrochloride ophthalmic solution 0.1% compared with cromolyn sodium ophthalmic solution 2% and levocabastine ophthalmic solution 0.05% as treatment for seasonal allergic conjunctivitis in children

STUDY SITE(S)
Europe and Australia

PATIENTS
Study 1: 30 children (mean age of 7.9 years, range: 4 to 11 years); study 2: 22 children (mean age of 8.6 years, range: 5 to 11 years); patients required to have a history of seasonal allergic conjunctivitis, positive reactions to common local grass pollens, current complaint of itching and conjunctival redness in both eyes

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); cromolyn sodium ophthalmic solution 2% and levocabastine ophthalmic solution 0.05% (Novartis Ophthalmics)

KEY ENDPOINT(S)
Primary efficacy variables: ocular itching and conjunctival redness; secondary efficacy variables: chemosis and eyelid swelling; study 2 also included patient self-ratings of ocular redness and nasal symptoms; physician's impression scale tolerability assessments based on visual acuity, pupil diameter, intraocular pressure, and a dilated fundus examination; 3 (study 1 only), 7, 14, 30, and 42 days after commencing treatment

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% was more effective than both cromolyn sodium 2% and levocabastine 0.05% in controlling ocular signs and symptoms of seasonal allergic conjunctivitis in children, and was well tolerated when administered twice daily for 6 weeks.

Conjunctival redness was significantly less intense with olopatadine 0.1% than cromolyn sodium 2% and levocabastine 0.05% during peak pollen periods.

†This study was supported by Alcon. One investigator, Darell Turner, is an Alcon employee.

STUDY RESULTS#

IMPROVEMENT IN SIGNS AND SYMPTOMS

- In study 1, ocular itching (P = 0.010) and conjunctival redness (P=0.003), were significantly less intense with olopatadine 0.1% than with cromolyn sodium 2% during the peak and declining pollen periods (**Table 1**)
- In study 2, conjunctival redness seen on slit-lamp examination (P = 0.040) was significantly less intense with olopatadine 0.1% than levocabastine 0.05% during the peak pollen period (**Table 2**)
- In both studies, patients diaries showed significant differences between treatments only during declining pollen periods, with superiority reported for olopatadine 0.1% for ocular redness in study 1 (P=0.019) and for ocular itching in study 2 (P=0.031)

ADVERSE EVENTS

- All three treatments were well tolerated in both studies
- Overall, 9 children experienced 10 adverse events (AEs); none of the AEs were serious or caused discontinuation of treatment; AEs occurred in 4 olopatadine 0.1% patients, 1 levocabastine 0.05% patients, and 5 cromolyn sodium 2% patients
- Only 1 AE, a mild ocular discharge, was considered to be related to treatment (olopatadine 0.1%)

Table 1. Improvements in signs and symptoms (primary efficacy variables) in study 1 (N = 30). Adapted from Ciprandi et al. *Curr Ther Res Clin Exp.* 2004;65:186-199.

Parameter/Study Drug	Peak Pollen Period	Declining Pollen Period
Symptoms and Signs (primary efficacy variables)		
Itching, self-rated*		
Olopatadine 0.1%	1.95†	0.92†
Levocabastine 0.05%	3.08†	2.41†
P-value‡	0.010	0.010
Redness, slit-lamp§		
Olopatadine 0.1%	1.04†	0.64†
Levocabastine 0.05%	1.90†	1.56†
P-value‡	0.003	0.013

Table 2. Improvements in signs and symptoms (primary efficacy variables) in study 2 (N = 22). Adapted from Borazan et al. Ciprandi et al. *Curr Ther Res Clin Exp.* 2004;65:186-199.

Parameter/Study Drug	Peak Pollen Period	Declining Pollen Period
Symptoms and Signs (primary efficacy variables)		
Itching, self-rated*		
Olopatadine 0.1%	2.40†	1.00†
Levocabastine 0.05%	3.04†	2.28†
P-value‡	0.209	0.029
Redness, slit-lamp§		
Olopatadine 0.1%	0.95†	0.53†
Levocabastine 0.05%	1.77†	1.33†
P-value‡	0.040	0.032

**Response to the question, "How often during the last 3 days did your eyes itch enough that you wanted to rub them?" Scale: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = very frequently. †P < 0.05 versus day 0 (t test). ‡Between-treatment difference (t tests, assuming homogeneous variance). §Scale: 0 = baseline, no dilatation of vessels, to 4.0 = beefy, tomato-red vessels; total involvement of all quadrants and straight through to the limbus 360°.*

#Results for endpoints outside FDA approved indications for use are not included.

Clinical Efficacy of Olopatadine Vs Epinastine Ophthalmic Solution in the Conjunctival Allergen Challenge Model

Lanier et al. *Curr Med Res Opin.* 2004;20:1227-1233

OVERVIEW

STUDY DESIGN
Prospective, randomized, double-masked, contralaterally-controlled, single center allergen challenge study

STUDY PURPOSE
To compare the clinical efficacy of olopatadine hydrochloride ophthalmic solution 0.1% and epinastine hydrochloride ophthalmic solution 0.05% in the treatment of itching and conjunctival redness in the conjunctival allergen challenge model

STUDY SITE(S)
United States

PATIENTS
Sixty-six (66) patients (mean age 44.4 years) who responded to conjunctival challenge received olopatadine 0.1% in one eye, epinastine 0.05% in the fellow eye (primary analysis group, n=53); olopatadine 0.1% in one eye, placebo in fellow eye (n=6); or epinastine 0.05% in one eye, placebo in fellow eye (n=7)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); epinastine hydrochloride ophthalmic solution 0.05% (Allergan, Inc)

KEY ENDPOINT(S)
Subjective itching assessed 3, 5 and 7 minutes post challenge, objective redness and chemosis assessed at 10, 15 and 20 minutes post challenge)

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1% was significantly more effective than epinastine 0.05% in controlling itching, redness associated with allergic conjunctivitis in the conjunctival allergen challenge model.

Mean itching and conjunctival redness scores were -0.19 (P=0.003) and -0.52 (P<0.001) lower, respectively, with olopadatine 0.1% than the contralateral epinastine treated eyes.

STUDY RESULTS#

PRIMARY OUTCOMES

- In the primary analysis group, olopatadine 0.1%-treated eyes had significantly lower mean itching scores than did the contralateral epinastine 0.05% -treated eyes at 5 minutes and 7 minutes; mean differences in scores were -0.21 at 5 minutes (P=0.049) and -0.33 at 7 minutes (P=0.005) (**Figure 1**)
- At all time points, olopatadine 0.1%-treated eyes had significantly lower conjunctival redness scores than the contralateral epinastine 0.05%-treated eyes; mean difference in scores were -0.50 (P<0.001) at 10 minutes, -0.52 (P<0.001) at 15 minutes, and -0.53 (P<0.001) at 20 minutes (**Figure 2**)

ADDITIONAL OUTCOMES

- Olopatadine 0.1%-treated eyes had significantly lower ciliary redness and episcleral redness scores than the epinastine 0.05%-treated eyes
- Separate subgroup analyses by gender and type of allergen used did not reveal significant differences compared with the primary analyses
- Advantages of both olopatadine 0.1% and epinastine 0.05% compared to placebo were demonstrated in all comparisons, with the exception of the 20-minute redness assessment for epinastine 0.05%
- There were no serious adverse events in this study; in the olopatadine 0.1%/ epinastine 0.05% treatment group, one subject reported an adverse event of transient stinging lasting approximately 1 minute in the epinastine 0.05%-treated eye

Figure 1. Comparison of mean ocular itching scores between olopatadine 0.1% and epinastine 0.05% after conjunctival allergen challenge (n = 53). Baseline itching scores were elicited prior to drug administration.

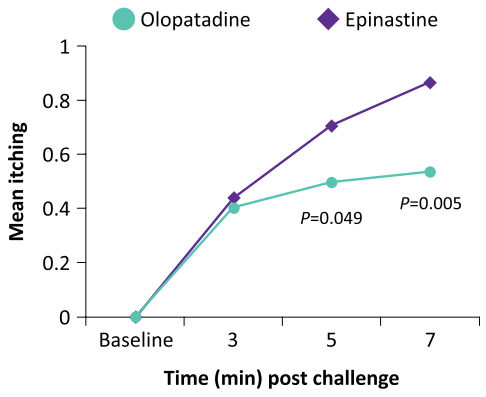
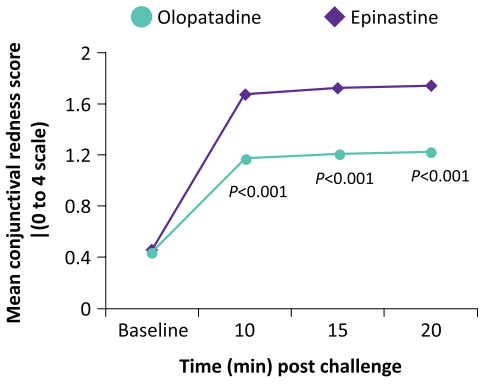


Figure 2. Comparison of mean conjunctival redness scores between olopatadine 0.1% and epinastine 0.05% after conjunctival allergen challenge (n = 53). Baseline conjunctival redness scores were elicited prior to drug administration.



#Results for endpoints outside FDA approved indications for use are not included.

Efficacy and Response with Olopatadine Versus Epinastine in Ocular Allergic Symptoms: A Post Hoc Analysis of Data from a Conjunctival Allergen Challenge Study

Finegold et al. *Clin Ther.* 2006;28:1630-1638

OVERVIEW

STUDY DESIGN
Post hoc analysis of data from a previous single-center, prospective, randomized, double-masked, contralateral-controlled study using the conjunctive allergen challenge (CAC) model

STUDY PURPOSE
To more precisely evaluate the efficacy of olopatadine hydrochloride ophthalmic solution 0.1% and epinastine hydrochloride in alleviating various levels of severity of ocular itching and conjunctival redness, and to determine whether there were any significant differences in the number of responders to treatment

STUDY SITE(S)
United States

PATIENTS
Sixty-six (66) subjects with allergic conjunctivitis; mean age of 44.38 years (range: 20 to 71 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); epinastine hydrochloride ophthalmic solution 0.05% (Allergan, Inc.)

KEY ENDPOINT(S)
Original study: itching, redness, and chemosis; post hoc analysis: stratification of eyes based on pretreatment severity, analysis of response rate

ANALYSIS AND CONCLUSIONS

The symptom severity analysis in this study suggested that olopatadine 0.1% may more effectively treat ocular itching (as measured using symptom severity scores) than did epinastine 0.05% in patients with ocular allergy regardless of severity.

The responder analysis suggested that olopatadine 0.1% was more effective (as measured using symptom severity scores) than epinastine 0.05% at completely resolving ocular itching and redness associated with allergic conjunctivitis. Further larger controlled trials are needed to confirm these results.

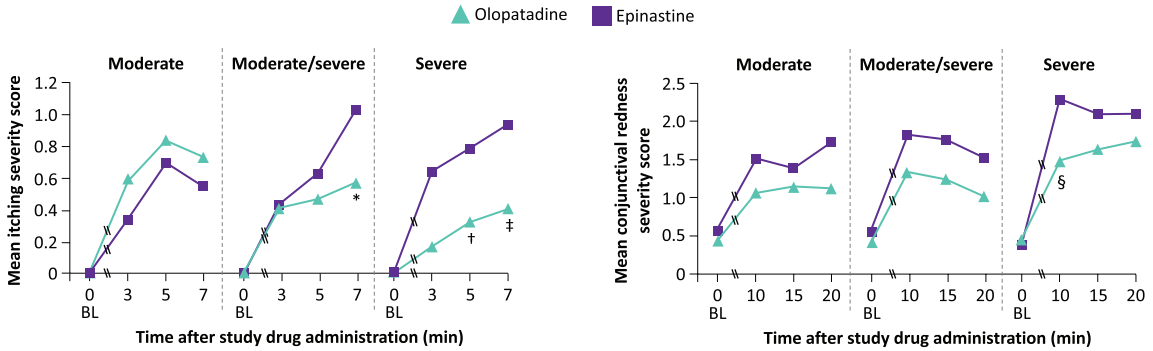
STUDY RESULTS#

SYMPTOM SEVERITY ANALYSIS
- Olopatadine 0.1%-treated eyes exhibited lower mean itching scores than epinastine 0.05%-treated eyes in the moderate/severe and severe groups at all 3 time points (3, 5, and 7 minutes)
- Olopatadine 0.1%-treated eyes had mean conjunctival redness scores similar to epinastine 0.05%-treated eyes in all severity groups at all time points (10, 15, and 20 minutes) except in the severe group at 10 minutes (**Figure 1**)

RESPONDER ANALYSIS
- For itching, the proportion of responders was greater in the olopatadine 0.1% group versus the epinastine 0.05% group 7 minutes after challenge
- For conjunctival redness, the proportion of responders was greater with olopatadine 0.1% treatment versus epinastine 0.05% treatment at 15 and 20 minutes after challenge (15 minutes, 12 [22.6%] vs 1 [1.9%]; 20 minutes, 10 [18.9%] vs 1 [1.9%])

ADVERSE EVENTS
- There were no serious adverse events reported in this study
- One patient in the olopatadine 0.1%/epinastine 0.05% treatment group reported mild, transient stinging lasting approximately 1 minute in the epinastine-treated eye immediately on instillation

Figure 1. Mean severity scores for (A) itching and (B) conjunctival redness at visit 3 by severity category and treatment. Includes the 53 patients (106 eyes) who received olopatadine 0.1% in 1 eye and epinastine 0.05% in the other and had a conjunctival redness severity score ≥2 at visit 2. Scale: 0 = none to 4 = severe; half-point increments allowed.



#Results for endpoints outside FDA approved indications for use are not included.

Comparison of the Efficacy of Olopatadine Hydrochloride 0.1% Ophthalmic Solution and Artificial Tears in Seasonal Allergic Conjunctivitis

Kamis et al. *Acta Ophthalmol Scand.* 2006;84:148-149

OVERVIEW

STUDY DESIGN
Single-center, randomized, prospective study using an environmental model

STUDY PURPOSE
To compare the efficacy of olopatadine hydrochloride ophthalmic solution 0.1% with that of artificial tears

STUDY SITE(S)
Turkey

PATIENTS
Fifty-one (51) patients with symptoms and signs of seasonal allergic conjunctivitis; mean age 24.8 years (range: 14 to 49 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); artificial tears (Tears Naturale II®, Alcon Vision, LLC)

KEY ENDPOINT(S)
Conjunctival hyperemia, chemosis, mucous discharge and lid edema scored by slit-lamp examination; ocular itching and lacrimation scored by questionnaire.

ANALYSIS AND CONCLUSIONS

The scores for eyes receiving olopatadine 0.1% treatment were significantly lower at the end of the first week.

Results from this study using an environmental model confirm findings of previous conjunctival allergen challenge studies assessing efficacy of olopatadine 0.1% in a variety of settings, and are also consistent with patient preferences reported in other trials.

STUDY RESULTS#

SIGNS AND SYMPTOMS

- Itching and hyperemia scores for eyes receiving olopatadine 0.1% were already significantly lower at the end of the first week
- Mean values for ocular itching decreased from 2.58 at baseline to 1.67 at week 1, and for conjunctival hyperemia decreased from 2.01 to 1.13
- Mean values for ocular itching decreased from 2.58 at baseline to 0.93 at week 4, and for conjunctival hyperemia decreased from 2.01 to 0.56 (**Table 1**)

Table 1. Ocular signs and symptoms at baseline and at week 4. Adapted from Kamis et al. *Acta Ophthalmol Scand.* 2006;84:148-149.

Parameter	Baseline Mean score (range)	Week 4 Mean score (range)
Itching		
Olopatadine 0.1%	2.59 (1.5–4.0)	0.93 (0.0–2.0)
Artificial tears	2.59 (1.5–4.0)	1.98 (0.5–3.5)
P-value*	1.000	<0.001
Hyperemia		
Olopatadine 0.1%	2.01 (1.0–3.5)	0.56 (0.0–1.0)
Artificial tears	2.01 (1.0–3.5)	1.49 (0.5–3.0)
P-value*	1.000	<0.001

**Mann–Whitney U-test.*

#*Results for endpoints outside FDA approved indications for use are not included.*

Efficacy of Olopatadine HCl 0.1%, Ketotifen Fumarate 0.025%, Epinastine HCl 0.05%, Emedastine 0.05% and Fluorometholone Acetate 0.1% Ophthalmic Solutions for Seasonal Allergic Conjunctivitis: A Placebo-Controlled Environmental Trial

Signs and Symptoms

Ocular Surface Variables

Borazan et al. *Acta Ophthalmol.* 2009;87:549-554

OVERVIEW

STUDY DESIGN
Prospective, randomized, double-blinded and placebo-controlled study

STUDY PURPOSE
To compare the clinical efficacy and ocular surface variables of olopatadine hydrochloride ophthalmic solution 0.1%, ketotifen fumarate 0.025%, epinastine hydrochloride 0.05%, emedastine difumarate 0.05% and fluorometholone acetate 0.1% in treating the signs and symptoms of seasonal allergic conjunctivitis

STUDY SITE(S)
Turkey

PATIENTS
One hundred (100) patients with seasonal allergic conjunctivitis; mean age 26.20 years, range: 10–55 years

STUDY AGENTS
Olopatadine hydrochloride 0.1% (Alcon Vision, LLC); ketotifen fumarate 0.025% (Alcon Vision, LLC); epinastine hydrochloride 0.05% (Allergan Pharmaceuticals Ltd); emedastine difumarate 0.05% (Alcon Vision, LLC); fluorometholone acetate 0.1% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Signs and symptoms of allergic conjunctivitis (itching, redness, tearing, chemosis and eyelid swelling) scored on a 4-point scale at baseline and then after 1 and 2 weeks of treatment; ocular surface variables were assessed by conjunctival impression cytology

ANALYSIS AND CONCLUSIONS

This study found that all of the agents were more effective than placebo in providing relief from the ocular signs and symptoms of seasonal allergic conjunctivitis at all time-points.

Olopatadine 0.1%, ketotifen fumarate 0.025%, epinastine hydrochloride 0.05% and emedastine difumarate 0.05% were more efficacious than the corticosteroid fluorometholone acetate 0.1% in decreasing itching and redness in patients with seasonal allergic conjunctivitis.

STUDY RESULTS#

IMPROVEMENT IN SIGNS AND SYMPTOMS

- At weeks 1 and 2, all study agents were significantly more effective than placebo in alleviating itching and redness (P<0.001) (**Table 1**)
- Ocular itching and conjunctival redness were significantly less improved in eyes in the fluorometholone acetate 0.1% group compared with all other groups at all control visits (**Table 1**)
- In the placebo-treated eyes, itching scores were significantly lower on days 7 and 14 compared with baseline scores

Table 1. Improvement in signs and symptoms scores of all study agents versus placebo at week 2. Adapted from Borazan et al. *Acta Ophthalmol.* 2009;87:549-554.

	Itching	Redness
Olopatadine 0.1%		
Baseline	2.60 (2-3)	2.60 (2-3)
Week 2	0.60 (0-1)	0.80 (0-1)
P-value vs placebo	P<0.001	P<0.001
Ketotifen fumarate 0.025%		
Baseline	2.70 (2-3)	2.75 (2-3)
Week 2	0.80 (0-1)	0.95 (0-2)
P-value vs placebo	P<0.001	P<0.001
Epinastine hydrochloride 0.05%		
Baseline	2.55 (2-3)	2.65 (2-3)
Week 2	1.00 (1-1)	1.10 (1-2)
P-value vs placebo	P<0.001	P<0.001
Emedastine difumarate 0.05%		
Baseline	2.60 (2-3)	2.70 (2-3)
Week 2	1.00 (1-1)	1.25 (1-2)
P-value vs placebo	P<0.001	P<0.001
Fluorometholone acetate 0.1%		
Baseline	2.60 (2-3)	2.70 (2-3)
Week 2	1.50 (1-2)	1.75 (1-2)
P-value vs placebo	P<0.001	P<0.001

Data are given as median (range).

#Results for endpoints outside FDA approved indications for use are not included.

Loteprednol Etabonate Suspension 0.2% Administered QID Compared with Olopatadine Solution 0.1% Administered BID in the Treatment of Seasonal Allergic Conjunctivitis: A Multicenter, Randomized, Investigator-Masked, Parallel Group Study in Chinese Patients

Gong et al. *Clin Ther.* 2012;34:1259-1272

OVERVIEW

STUDY DESIGN
Multicenter, randomized, investigator-masked, parallel group study

STUDY PURPOSE
To compare the efficacy and tolerability of loteprednol etabonate ophthalmic suspension 0.2% and olopatadine hydrochloride ophthalmic solution 0.1% in Chinese patients

STUDY SITE(S)
China

PATIENTS
Three hundred (300) patients with acute seasonal allergic conjunctivitis; mean age of 40.6 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); loteprednol etabonate ophthalmic suspension 0.2% (Bausch + Lomb)

KEY ENDPOINT(S)
Primary efficacy endpoints: change from baseline in ocular itching and bulbar conjunctival injection (redness) at day 15; tolerability outcomes: incidence of adverse events (AEs), biomicroscopy findings, visual acuity, and intraocular pressure (IOP)

ANALYSIS AND CONCLUSIONS

Results from this study in patients with seasonal allergic conjunctivitis suggest that loteprednol etabonate 0.2% was noninferior to olopatadine 0.1% with respect to improvement in ocular itching and bulbar conjunctival injection.

Both treatments were well tolerated; ocular AEs were few and similar between treatment groups, and there were no clinically significant biomicroscopy or visual acuity findings in either treatment group.

STUDY RESULTS

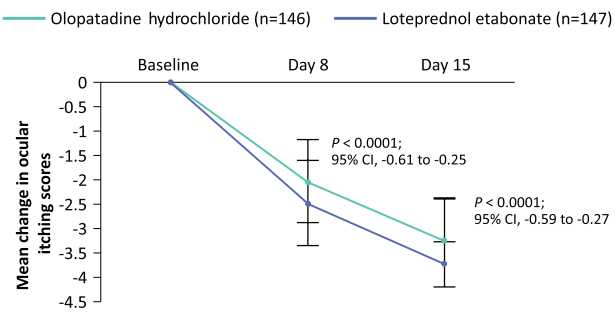
SIGNS AND SYMPTOMS

- Mean (SD) change from baseline at day 15 in the loteprednol etabonate 0.2% and olopatadine 0.1% treatment groups, respectively, was -3.74 (0.47) and -3.28 (0.91) for ocular itching P<0.0001) (**Figure 1**) and -1.91 (0.52) and -1.71 (0.59) for bulbar conjunctival injection (P=0.0006) (**Figure 2**)
- At day 15, the 95% CI for the differences in change from baseline in ocular itching (-0.59 to -0.27) (**Figure 1**) and bulbar conjunctival injection (-0.27 to -0.08) (**Figure 2**) was less than the prespecified noninferiority limit of 0.3, indicating noninferiority of loteprednol etabonate 0.2% to olopatadine 0.1% for these end points
- Treatment differences in change from baseline were significantly better with loteprednol etabonate 0.2% compared with olopatadine 0.1% at day 15 for both end points (P≤0.0006)
- The proportion of patients with complete resolution of ocular itching was 74.6% and 50.7% in the loteprednol etabonate 0.2% and olopatadine 0.1% groups, respectively, and the proportion with complete resolution of bulbar conjunctival injection was 78.3% and 61.3%, respectively, (P≤0.00269 for both outcomes)

ADVERSE EVENTS

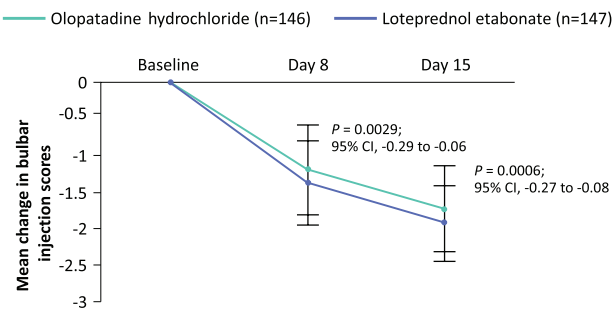
- Both loteprednol etabonate 0.2% and olopatadine solution 0.1% were well tolerated
- A total of 5 patients (3.3%) in the loteprednol etabonate 0.2% group and 2 patients (1.3%) in the olopatadine 0.1% group reported ≥1 treatment-emergent adverse event (TEAE)
- Ocular TEAEs were reported by 3 patients (2.0%) in the loteprednol etabonate 0.2% group and 2 patients (1.3%) in the olopatadine 0.1% group
- There were no clinically significant biomicroscopy or visual acuity findings, and no patient experienced a clinically significant increase in IOP (≥10 mm Hg)

Figure 1. Change in mean ocular itching from baseline at days 8 and 15. Negative values indicate changes in favor of loteprednol etabonate 0.2%.



Values shown as mean (SD). CI and P-values were calculated using least squares mean.

Figure 2. Change in mean bulbar injection from baseline at days 8 and 15. Negative values indicate changes in favor of loteprednol etabonate 0.2%.



Values shown as mean (SD). CI and P-values were calculated using least squares mean.

Efficacy of Epinastine Hydrochloride Ophthalmic Solution in Allergic Conjunctivitis by Conjunctival Cedar Pollen Allergen Challenge

Fujishima et al. *Ann Allergy Asthma Immunol.* 2014;113:476-481

OVERVIEW

STUDY DESIGN
Randomized single-center, double-masked comparison study using a conjunctival allergen challenge (CAC) test with cedar pollen

STUDY PURPOSE
To show the superiority of epinastine ophthalmic solution 0.05% to placebo) and noninferiority to olopatadine ophthalmic solution 0.1% for cedar pollen antigen-induced ocular itching and conjunctival hyperemia

STUDY SITE(S)
Japan

PATIENTS
Asymptomatic subjects with seasonal allergic conjunctivitis randomized into 3 groups (n = 87) to evaluate superiority to placebo (visits 4-6) and 2 groups (n = 86) to evaluate noninferiority to olopatadine 0.1% (visit 7); mean age across treatment groups of 39.0 to 39.7 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); epinastine ophthalmic solution 0.05% (Allergan, Inc.)

KEY ENDPOINT(S)
Ocular itching and conjunctival hyperemia after CAC when medication was instilled at 15 minutes, 4 and 8 hours before CAC (visits 4-6) and 4 hours before CAC (visit 7)

ANALYSIS AND CONCLUSIONS

Epinastine was superior to placebo and rapidly effective against the symptoms of allergic conjunctivitis, with effects maintained for 8 hours after instillation, and was also noninferior to olopatadine with respect to ocular itching and conjunctival hyperemia.

The investigators concluded that epinastine should be considered an effective and rational choice in the treatment of cedar pollen allergic conjunctivitis in Japan.

STUDY RESULTS

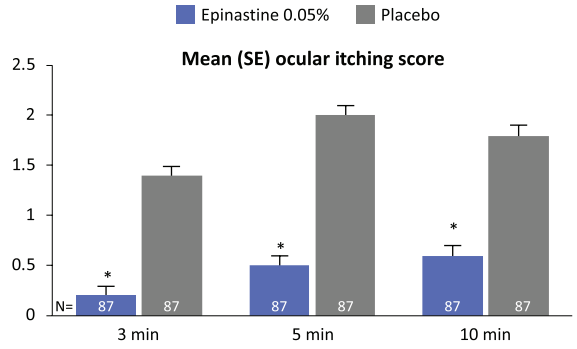
SIGNS AND SYMPTOMS

- For the primary end point, epinastine 0.05% showed superiority to placebo for the inhibition of ocular itching (P<0.001) (**Figure 1**) and conjunctival hyperemia (**Figure 2**) (P<0.001) induced at 4 hours after the dose (equivalent to 4x daily dosing)
- For the secondary endpoints, epinastine 0.05% inhibited ocular itching to a significantly greater degree than placebo at 15 minutes (P<0.001) and 8 hours (P<0.001), and conjunctival hyperemia at 15 minutes (P<0.001) and 8 hours (P=0.003)
- In addition, epinastine 0.05% demonstrated noninferiority to olopatadine 0.1% for ocular itching and conjunctival hyperemia
  - The difference in the ocular itching score (epinastine minus olopatadine) was -0.1 ± 0.1, and the difference in conjunctival hyperemia score was -0.3 ± 0.3
  - In both analyses the upper limit of the confidence interval was lower than the noninferiority margin (0.5), thus verifying the noninferiority of epinastine 0.05% to olopatadine 0.1%

ADVERSE EVENTS

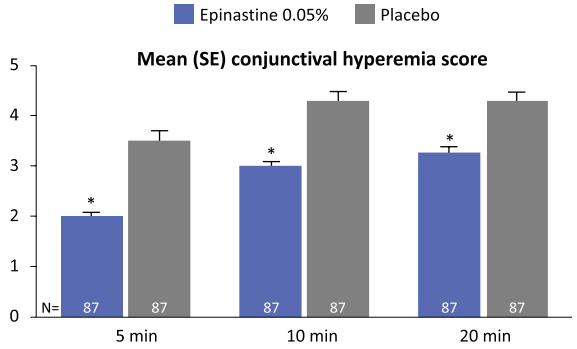
- Adverse events were reported in 5 of the 87 subjects included in the safety analysis set (nasopharyngitis, urticaria, wound formation, oropharyngeal discomfort, and conjunctivitis); all events were considered unrelated to the study drug
- All events were mild or moderate in severity and resolved or were alleviated during the study period without leading to discontinuation of the study; no serious adverse events were reported

Figure 1. Mean ocular itching scores (mean ± SE) after a conjunctival allergen challenge at 4 hours after epinastine 0.05% or placebo instillation by assessment time.



*P<0.0001.

Figure 2. Mean conjunctival hyperemia scores (mean ± SE) after a conjunctival allergen challenge at 4 hours after epinastine 0.05% or placebo instillation by assessment time.



*P<0.0001.

Efficacy of Olopatadine Versus Epinastine for Treating Allergic Conjunctivitis Caused by Japanese Cedar Pollen: A Double-Blind Randomized Controlled Trial

Signs and Symptoms

Adverse Events

Fukushima et al. *Adv Ther*. 2014;31:1045-1058*

OVERVIEW

STUDY DESIGN
Phase IV double-blind randomized controlled clinical trial

STUDY PURPOSE
To compare the efficacy and safety at onset of olopatadine versus epinastine in healthy Japanese adults with a history of allergic conjunctivitis to Japanese cedar pollen using the conjunctival allergen challenge (CAC)

STUDY SITE(S)
Japan

PATIENTS
Fifty (50) healthy Japanese subjects ≥20 years of age with a history of allergic conjunctivitis to Japanese cedar pollen

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); epinastine hydrochloride ophthalmic solution 0.05% (Allergan, Inc)

KEY ENDPOINT(S)
Severity of ocular itching at 5, 7, and 15 minutes after CAC, severity of conjunctival hyperemia at 7, 15, and 20 minutes after CAC

ANALYSIS AND CONCLUSIONS

The results of this study suggest that olopatadine 0.1% is more effective than epinastine 0.05% at reducing the symptoms of Japanese cedar pollen-induced allergic conjunctivitis in the CAC tests.

Prospective randomized controlled trials in real-life settings are needed to confirm these results and the efficacy and safety of longer term administration of olopatadine 0.1%.

*This study was supported by Alcon.

STUDY RESULTS

OCULAR ITCHING

- Seven minutes after allergen challenge, the mean ocular itching score was 0.23 ± 0.31 in olopatadine 0.1% -treated eyes compared with 0.37 ± 0.44 in epinastine 0.05%-treated eyes; the treatment difference was statistically significant in favor of olopatadine 0.1% (primary endpoint, P= 0.0462) (**Figure 1**)
- A statistically significant difference of −0.17 in favor of olopatadine 0.1% was also observed 15 minutes after allergen challenge (P=0.0432)

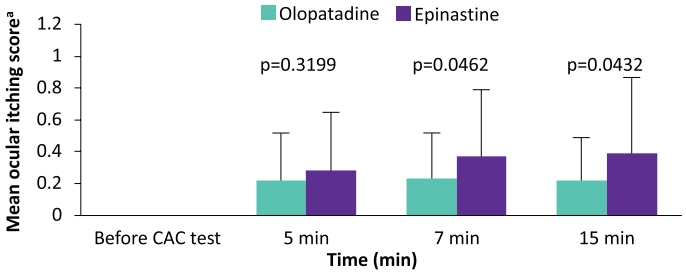
CONJUNCTIVAL HYPEREMIA

- Twenty minutes after allergen challenge, mean conjunctival hyperemia score was 0.89 ± 0.88 in olopatadine 0.1% -treated eyes and 1.12 ± 0.95 in epinastine 0.05%-treated eyes; the treatment difference was statistically significant in favor of olopatadine 0.1% (secondary endpoint P=0.0273) (**Figure 2**)
- A statistically significant difference of −0.12 in favor of olopatadine 0.1% was also observed 7 minutes after allergen challenge (P=0.0010)

ADVERSE EVENTS

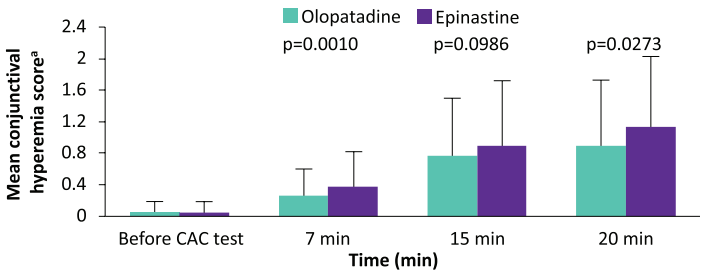
- There were no adverse events during the study, and no subjects withdrew from the study because of adverse events
- No abnormal findings in slit lamp biomicroscopy, undilated fundoscopy, or physical examination were observed at any visit, nor were there significant changes in visual acuity or vital signs between study visits

Figure 1. Effects of olopatadine 0.1% and epinastine 0.05% on mean ocular itching score at 5, 7, and 15 minutes after allergen administration (Japanese cedar pollen).



[a]Mean ocular score was assessed using a 5-point scale with 0.5-unit increments ranging from 0 to 4. Values are mean ± standard deviation.
CAC, conjunctival allergen challenge; SD, standard deviation.

Figure 2. Effects of olopatadine 0.1% and epinastine 0.05% on conjunctival hyperemia scores at 7, 15, and 20 minutes after allergen administration (Japanese cedar pollen). cedar pollen).



[a]Mean conjunctival hyperemia score was assessed using a 5-point scale with 0.5-unit increments ranging from 0 to 4. Values are mean ± standard deviation.
CAC, conjunctival allergen challenge; SD, standard deviation.

Efficacy of Olopatadine Hydrochloride 0.1%, Emedastine Difumarate 0.05%, and Loteprednol Etabonate 0.5% for Chinese Children with Seasonal Allergic Conjunctivitis: A Randomized Vehicle-Controlled Study

Liu et al. *Int Forum Allergy Rhinol.* 2017;7:393-398

OVERVIEW

STUDY DESIGN
Three-visit, prospective, single-blind, randomized, placebo-controlled, single-center study

STUDY PURPOSE
To compare the clinical efficacy of olopatadine hydrochloride ophthalmic solution 0.1%, emedastine difumarate ophthalmic solution 0.05%, loteprednol etabonate ophthalmic suspension 0.5%, and vehicle for treating seasonal allergic conjunctivitis in Chinese children

STUDY SITE(S)
China

PATIENTS
One hundred sixty (160) eyes of 80 children with seasonal allergic conjunctivitis; mean age of 6.33 years (range: 5 to 10 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); emedastine difumarate ophthalmic solution 0.05% (Alcon Vision, LLC); loteprednol etabonate ophthalmic suspension 0.5% (Bausch + Lomb)

KEY ENDPOINT(S)
Signs and symptoms of seasonal allergic conjunctivitis (itching, photophobia, blinking, redness, edema, papilla, follicle) on day 8 (±1 day) and day 15 (±2 days) after treatment

ANALYSIS AND CONCLUSIONS

Olopatadine 0.1%, emedastine 0.05%, and loteprednol etabonate 0.5% were all found to be more effective than vehicle in reducing the signs and symptoms of seasonal allergic conjunctivitis, but there was no statistical significance among the treatment groups.

Olopatadine, emedastine, and loteprednol etabonate were equally effective in a small sample of children.

STUDY RESULTS#

SIGNS AND SYMPTOMS

- Olopatadine 0.1%, emedastine 0.05%, and loteprednol etabonate 0.5% had similar efficacy in reducing the signs and symptoms of seasonal allergic conjunctivitis (**Table 1**)
- At weeks 1 and 2 after treatment, changes in ocular itching were statistically significant for all active treatments vs vehicle (P<0.05), and there were no statistically significant differences among the treatment groups
  - Mean itching scores for olopatadine 0.1%, emedastine 0.05%, and loteprednol etabonate 0.5% after 2 weeks were 0.28 ± 0.64, 0.13 ± 0.39, and 0.05 ± 0.22, respectively, vs 0.70 ± 0.62 for vehicle
- Similarly, at weeks 1 and 2 after treatment, changes in signs such as redness were statistically significant for all active treatments vs vehicle (P<0.05), and there were no statistically significant differences among the treatment groups
  - Mean redness scores for olopatadine 0.1%, emedastine 0.05%, and loteprednol etabonate 0.5% after 2 weeks were 0.43 ± 0.34, 0.45 ± 0.36, and 0.15 ± 0.29, respectively, vs 0.65 ± 0.37 for vehicle

Table 1. Change in ocular sign and symptoms after 2 weeks of treatment. Values are shown as mean ± SD or P-value (95% CI), as indicated. Adapted from Liu et al. *Int Forum Allergy Rhinol.* 2017;7:393-398.

	Mean ± SD	Olopatadine (n=20)	Emedastine (n=20)	LE (n=20)	Vehicle (n=20)
Olopatadine					
Itching	0.28 ± 0.64	–	0.581 (−0.21 to 0.37)	0.096 (−0.44 to 0.52)	0.030 (−0.73 to 0.16)
Redness	0.43 ± 0.34	–	0.466 (−0.07 to 0.16)	0.340 (−0.06 to 0.17)	0.000 (−0.72 to −0.49)
Emedastine					
Itching	0.13 ± 0.39	0.581 (−0.37 to 0.21)	–	0.269 (−0.13 to 0.45)	0.000 (−0.81 to 0.24)
Redness	0.45 ± 0.36	0.466 (−0.16 to 0.07)	–	0.820 (−0.14 to 0.10)	0.000 (−0.77 to −0.01)
LE					
Itching	0.05 ± 0.22	0.096 (−0.52 to 0.04)	0.269 (−0.45 to 0.13)	–	0.000 (−0.97 to 0.40)
Redness	0.15 ± 0.29	0.340 (−0.17 to −0.06)	0.820 (−0.13 to 0.10)	–	0.000 (−0.78 to −0.55)
Vehicle					
Itching	0.70 ± 0.62	0.003 (−0.16 to 0.73)	0.000 (−0.24 to 0.81)	0.000 (−0.40 to 0.97)	–
Redness	0.65 ± 0.37	0.000 (0.49 to 0.72)	0.000 (0.53 to 0.77)	0.000 (0.55 to 0.78)	–

CI = confidence interval; LE = loteprednol etabonate; SD = standard deviation

#Results for endpoints outside FDA approved indications for use are not included.

Observer-Masked Trial Comparing Efficacy of Topical Olopatadine (0.1%), Bepotastine (1.5%), and Alcaftadine (0.25%) in Mild to Moderate Allergic Conjunctivitis

Signs and Symptoms

Adverse Events

Dudeja et al. *Indian J Ophthalmol.* 2019;67:1400-1404

OVERVIEW

STUDY DESIGN
Prospective, observer-masked clinical trial

STUDY PURPOSE
To directly compare the efficacy of three ophthalmic solutions: olopatadine hydrochloride 0.1%, alcaftadine 0.25%, and bepotastine besilate 1.5% administered twice daily

STUDY SITE(S)
India

PATIENTS
Forty-give (45) patients with mild to moderate allergic conjunctivitis presenting to an outpatient department; age range 10-40 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1% (Alcon Vision, LLC); alcaftadine ophthalmic solution 0.25% (Allergan plc); bepotastine besilate ophthalmic solution 1.5% (Bausch + Lomb)

KEY ENDPOINT(S)
Relief of signs and symptoms up to 1 month

ANALYSIS AND CONCLUSIONS

Olopatadine hydrochloride 0.1%, bepotastine 1.5%, and alcaftadine 0.25% administered twice daily were equally effective in resolving symptoms of mild to moderate allergic conjunctivitis, and most patients reported complete relief after 1 week.

All three study drugs also relieved signs of redness within 1 week.

STUDY RESULTS#

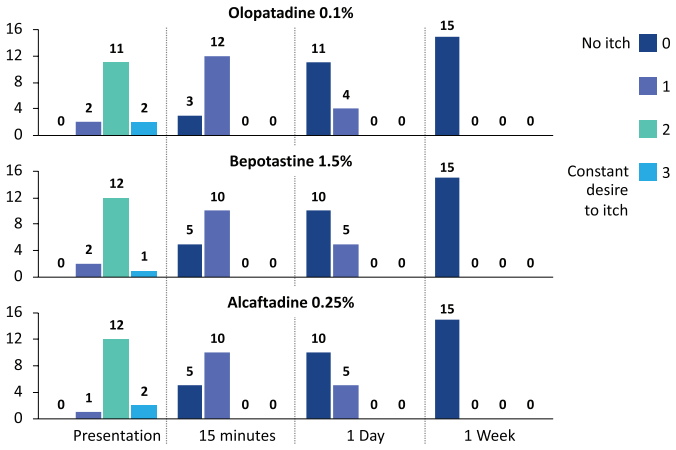
SIGNS AND SYMPTOMS

- The mean time for the beginning of itch relief was comparable for olopatadine 0.1%, bepotastine 1.5% and alcaftadine 0.25% groups (mean range of 5-15 minutes)
- All three medications produced statistically significant itch relief; symptomatic benefits started within minutes and complete relief of itching occurring within 1 week (**Figure 1**)
- Within 15 minutes of eyedrop instillation, all patients in the three treatment groups had either no or minimal itching (itch score of 0 or 1) (**Figure 1**)
- Olopatadine 0.1%, bepotastine 1.5% and alcaftadine 0.25% relieved other symptoms as well, including redness, producing complete symptomatic relief within 1 week
- Ocular signs such as limbal hyperemia did not respond to olopatadine 0.1%, bepotastine 1.5% or alcaftadine 0.25%

ADVERSE EVENTS

- All three medications were well-tolerated except for mild burning sensation noted by two olopatadine patients (13%), four bepotastine 1.5% patients (26%), and six alcaftadine 0.25% patients (40%); these events were transient in nature

Figure 1. Bar graphs showing distribution of itch scores (scale: 0 indicating no itch to 3 indicating constant desire to itch) for olopatadine 0.1%, bepotastine 1.5% and alcaftadine 0.25% patients at various time intervals.



#Results for endpoints outside FDA approved indications for use are not included.

Efficacy of Olopatadine Ophthalmic Solution 0.2% in Reducing Signs and Symptoms of Allergic Conjunctivitis

Signs and Symptoms

Adverse Events

Abelson et al. *Allergy Asthma Proc.* 2007;28:427-433

OVERVIEW

STUDY DESIGN
Double-masked, randomized by eye, parallel-group study using the conjunctival allergen challenge

STUDY PURPOSE
To evaluate the safety, efficacy, onset, and duration of action of olopatadine hydrochloride ophthalmic solution 0.2% in the treatment of allergic conjunctivitis

STUDY SITE(S)
United States

PATIENTS
Ninety (90) patients with a reported history of allergic conjunctivitis; mean age 39.5 years (range: 20-67 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Primary endpoint: ocular itch at onset and 16 hours after drug instillation; secondary endpoint: conjunctival redness, chemosis, and eyelid swelling; safety parameters

ANALYSIS AND CONCLUSIONS

This study demonstrated that once-daily dosing with olopatadine 0.2% reduced symptoms of ocular allergy itch with a rapid and prolonged duration of action.

Safety analyses indicated that olopatadine 0.2% was safe and well tolerated in subjects with a history of allergic conjunctivitis.

STUDY RESULTS#

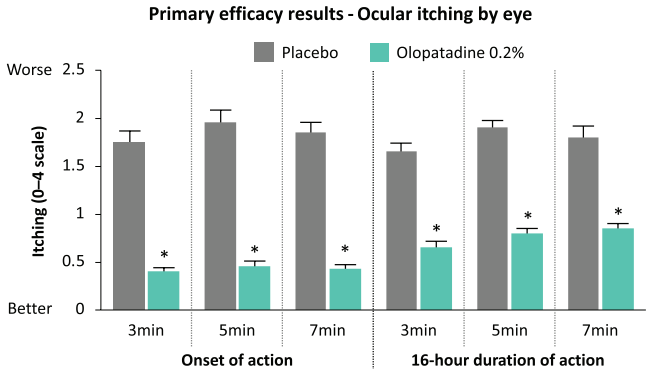
SIGNS AND SYMPTOMS

- For the primary endpoint of ocular itching, olopatadine 0.2% was significantly (P<0.001) more effective than placebo at all time points (3, 5 and 7 minutes postchallenge) at both onset and 16 hours after drug instillation (**Figure 1**)
- In a subgroup analysis of 44 patients who received olopatadine 0.2% in one eye and placebo in the contralateral eye, olopatadine 0.2% provided significantly greater improvement in:
  - ocular itching (P<0.001) at all three time points at onset and 16 hours after drug instillation

ADVERSE EVENTS

- Overall, 6 patients reported 8 adverse events; all adverse events during the study were mild or moderate and resolved with or without treatment except for two that were unrelated to treatment

Figure 1. Primary efficacy results. Comparison of mean ocular itching scores between olopatadine 0.2%-treated eyes and placebo-treated eyes after conjunctival allergen challenges.



*P < 0.05. Error bars represent standard error.

#Results for endpoints outside FDA approved indications for use are not included.

Safety and Tolerability of Olopatadine 0.2% in Children and Adolescents

Lichtenstein et al. *J Ocul Pharmacol Ther.* 2007;23:366-371

OVERVIEW

STUDY DESIGN
Six-week, randomized, double-masked safety evaluation

STUDY PURPOSE
To evaluate the safety of olopatadine hydrochloride ophthalmic solution 0.2% in children and adolescents 3-17 years of age

STUDY SITE(S)
United States

PATIENTS
One hundred twenty-six (126) subjects with asymptomatic eyes (age range 3 to 17 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Adverse events, visual acuity, ocular signs (slit-lamp assessments), dilated fundus examinations, intraocular pressure (IOP), pulse, and blood pressure

ANALYSIS AND CONCLUSIONS

This study demonstrated that olopatadine 0.2%, administered once a day, is safe and well tolerated in pediatric patients, based upon an assessment of adverse events as well as ocular and cardiovascular safety parameters.

The authors suggested that results of this study, coupled with previous efficacy data indicating a sufficient duration of action to manage the ocular allergic reaction on a once-daily dosing schedule, indicate that olopatadine 0.2% could represent a safe, effective once-daily treatment regimen.

STUDY RESULTS

ADVERSE EVENTS

- No serious adverse events (AEs) were reported during this study, and no subjects experienced any clinically relevant, treatment-related changes from baseline in visual acuity, dilated fundus examinations, IOP, pulse, or blood pressure
- The only AEs related to treatment were eye discomfort reported by 1 subject (1.1%) and hyperemia observed in 1 subject (1.1%) in the olopatadine 0.2% group (**Table 1**)
- No nonocular AEs related to therapy were reported during the study.
- One subject in the overall pediatric population discontinued study participation due to a nontreatment-related, mild-to-moderate AE (an adolescent with poison ivy rash diagnosed as dermatitis); none of the other AEs caused any other pediatric subjects to withdraw from the study
- All of the AEs reported in the 3–5-year-old group (n=37) were mild-to-moderate in severity and resolved either with or without treatment, with the exception of 1 case of unresolved corneal staining in the olopatadine 0.2% treatment group (**Table 2**); the staining, in the inferior region of the right eye, was mild and was considered to have been unrelated to the study medication

Table 1. Ocular adverse events in subjects ages 3 to 17 years by treatment and relationship to study

	Olopatadine 0.2% (n=88)						Placebo (n=28)					
	Related		Unrelated		Total		Related		Unrelated		Total	
Adverse event	n	%	n	%	n	%	n	%	n	%	n	%
Conjunctivitis[a]			1	1.1	1	1.1			1	2.6	1	2.6
Accidental injury									1	2.6	1	2.6
Hyperemia	1	1.1	1	1.1	2	2.3						
Tearing			1	1.1	1	1.1						
Eye discomfort	1	1.1			1	1.1						
Corneal staining			1	1.1	1	1.1						

[a]*Conjunctivitis cases were viral.*

Table 2. Ocular adverse events in pediatric subjects ages 3 to 5 years.

	Olopatadine 0.2% (n=26)						Placebo (n=11)					
	Related		Unrelated		Total		Related		Unrelated		Total	
Adverse event	n	%	n	%	n	%	n	%	n	%	n	%
Conjunctivitis[a]			1	3.8	1	3.8			1	9.1	1	9.1
Accidental injury									1	9.1	1	9.1
Eye discomfort	1	3.8			1	3.8						
Corneal staining			1	3.8	1	3.8						

[a]*Conjunctivitis cases were viral.*

A Comparison of Olopatadine 0.2% Ophthalmic Solution Versus Fluticasone Furoate Nasal Spray for the Treatment of Allergic Conjunctivitis

Rosenwasser et al. *Allergy Asthma Proc.* 2008;29:644-653

OVERVIEW

STUDY DESIGN
Single-center, randomized, placebo-controlled, parallel-treatment, four-visit conjunctival allergen challenge (CAC) study

STUDY PURPOSE
To assess the comparative efficacy of olopatadine hydrochloride ophthalmic solution 0.2% and the intranasal steroid fluticasone furoate at reducing the signs and symptoms of allergic conjunctivitis induced by the CAC model

STUDY SITE(S)
United States

PATIENTS
Sixty (60) subjects with a history of allergic conjunctivitis; mean age of 44.8 years (range: 19 to 69 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2% (Alcon Vision, LLC); fluticasone furoate nasal spray (GlaxoSmithKline)

KEY ENDPOINT(S)
Primary endpoint: ocular itching 3, 5 and 7 minutes post-CAC; additional endpoints: ocular redness, tearing, chemosis, and eyelid swelling 7, 15 and 20 minutes post-CAC

ANALYSIS AND CONCLUSIONS

This study demonstrated that olopatadine 0.2% was able to more effectively treat ocular itching due to allergic conjunctivitis compared with the nasal spray fluticasone furoate.

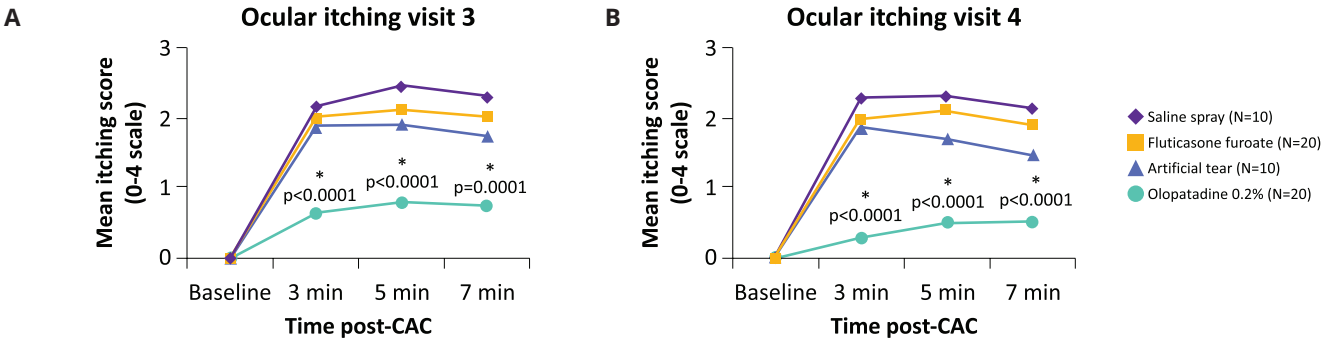
No significant difference in ocular allergy itch relief was observed with fluticasone furoate compared to both placebo nasal spray and placebo eye drop.

STUDY RESULTS[#]

PRIMARY EFFICACY VARIABLE

- Olopatadine 0.2%-treated eyes showed a greater reduction in ocular itching compared with all other treatment groups (**Figure 1**)
  - Statistical and clinical superiority of olopatadine 0.2% was observed over fluticasone furoate nasal spray and the placebo nasal spray at all post-CAC time points at both visit 3 (day 0) and visit 4 (day 7±3) (P<0.0001 and P<0.0005, respectively)
  - Olopatadine 0.2% showed statistical superiority over placebo eye drops at all time points at both visits for the reduction of ocular itching (P<0.009)
- No significant difference was observed for fluticasone furoate over placebo nasal spray or placebo eye drop

Figure 1. Mean ocular itching scores at (**A**) visit 3 (day 0) and (**B**) visit 4 (day 7 ± 3).



**Clinical significance versus fluticasone furoate.*

[#]Results for endpoints outside FDA approved indications for use are not included.

A Multicenter Evaluation of the Efficacy and Duration of Action of Alcaftadine 0.25% and Olopatadine 0.2% in the Conjunctival Allergen Challenge Model

Ackerman et al. *J Asthma Allergy*. 2013;6:43-52

OVERVIEW

STUDY DESIGN
Multicenter, double-masked, randomized, active-controlled and placebo-controlled clinical trial using the conjunctival allergen challenge model

STUDY PURPOSE
To evaluate the efficacy and duration of action of once-daily dosing with alcaftadine ophthalmic solution 0.25% and olopatadine hydrochloride ophthalmic solution 0.2% as compared with placebo in treating ocular itching, and to directly compare the efficacy of alcaftadine 0.25% with olopatadine itching associated with allergic conjunctivitis

STUDY SITE(S)
United States

PATIENTS
One hundred and twenty-seven (127) patients with allergic conjunctivitis (mean age 38.5 ± 13.2 years, range: 12 to 74 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2% (Alcon Vision, LLC); alcaftadine ophthalmic solution 0.25% (Allergan plc)

KEY ENDPOINT(S)
Primary efficacy measure was ocular itching at 3, 5, and 7 minutes post challenge; secondary endpoints, measured at 7, 15, and 20 minutes post challenge, included conjunctival, ciliary, and episcleral redness, lid swelling, chemosis, and tearing; duration of action measured at 16 and 24 hours post instillation of the medication

ANALYSIS AND CONCLUSIONS

Both alcaftadine 0.25% and olopatadine 0.2% provided highly effective relief of ocular itching at both 16 and 24 hours post-instillation, and both were generally safe and well tolerated.

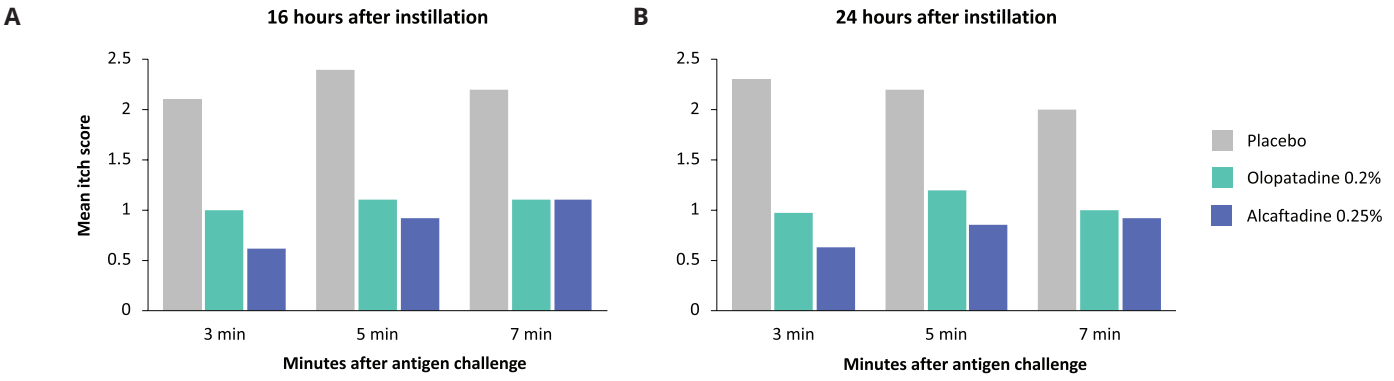
Treatment differences between the agents were most pronounced at the earliest time point (3 minutes post challenge) following conjunctival allergen challenge (16 hours), when alcaftadine 0.25% was statistically superior to olopatadine 0.2%, although the difference was not clinically relevant.

STUDY RESULTS#

OCULAR ITCHING

- For the primary endpoint of ocular itching, both alcaftadine 0.25% and olopatadine 0.2% were statistically superior to placebo at all three measured time points for both the 16-hour and 24-hour measures (P< 0.0001) (**Figure 1**)
- Eyes treated with alcaftadine 0.25% had numerically lower mean ocular itching scores than eyes treated with olopatadine 0.2% at every time point, and this difference was statistically significant at the 3-minute time point 16 hours post instillation (P=0.026). However, this difference was not clinically relevant (**Figure 1**)
- With respect to the percentage of subjects reporting minimal itch (a score of <1.0) at both the 16 and 24 hour assessments, the difference between treatments was greatest at 3 minutes (16 hours after instillation): 78% of subjects treated with alcaftadine 0.25% reported itch scores <1 as compared with 46% of those treated with olopatadine 0.2% (P=0.006)

Figure 1. Comparison of ocular itching scores at 16 hours (**A**) and at 24 hours (**B**) after instillation of treatment. Mean itching at 3, 5, and 7 minutes after allergen challenge.



#Results for endpoints outside FDA approved indications for use are not included.

Phase 3 Randomized Double-Masked Study of Efficacy and Safety of Once-Daily 0.77% Olopatadine Hydrochloride Ophthalmic Solution in Subjects With Allergic Conjunctivitis Using the Conjunctival Allergen Challenge Model

Signs and Symptoms

Adverse Events

McLaurin et al. *Cornea.* 2015;34:1245-1251

OVERVIEW

STUDY DESIGN
Five-week, multicenter, double-masked, phase 3, randomized trial

STUDY PURPOSE
To assess the efficacy and safety of once-daily olopatadine hydrochloride ophthalmic solution 0.77% in subjects with allergic conjunctivitis using the conjunctival allergen challenge (CAC) model

STUDY SITE(S)
United States

PATIENTS
Three hundred forty-five (345) patients with a history of allergic conjunctivitis and a confirmed positive bilateral CAC response; mean age across 4 treatment groups: 38.8 to 41.8 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.1%, 0.2%, and 0.7% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Primary: superiority of olopatadine 0.77% over all comparators on ocular itching at 24-hour duration of action and over vehicle only at onset of action (3, 5, and 7 minutes after CAC for both); Secondary: investigator-assessed conjunctival redness and total redness, and proportion of ocular itching responders

ANALYSIS AND CONCLUSIONS

This study demonstrated that olopatadine hydrochloride ophthalmic solution 0.77% had a rapid onset and prolonged duration of action (30 minutes and 24 hours post-drug administration).

It was superior to vehicle in alleviating allergic conjunctivitis-associated ocular itching and was well tolerated.

STUDY RESULTS#

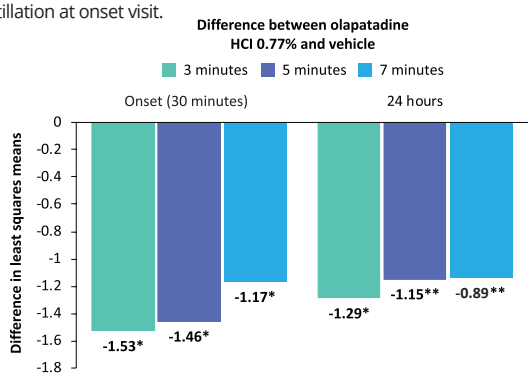
OCULAR ITCHING

- Olopatadine 0.77% was superior to the vehicle at alleviating ocular itching at all post-CAC time points at onset of action and at 24 hours (difference in means: -0.9 to -1.5; P<0.0001) (**Figure 1**)
- At 24 hours, olopatadine 0.77% provided statistically greater ocular itch relief versus olopatadine 0.2%, but the difference was not clinically relevant (3 and 5 minutes after CAC difference in means: -0.3 to -0.3, P<0.05)
- At 24 hours, olopatadine 0.77% provided significantly greater ocular itch relief versus olopatadine 0.1% (all 3 post-CAC time points; difference in means: -0.4 to -0.5; P<0.05) (**Figure 2**)

ADVERSE EVENTS

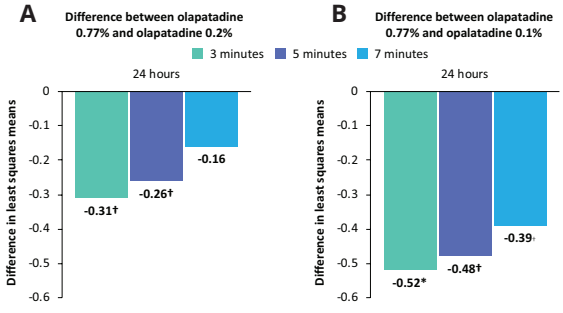
- Two subjects treated with olopatadine 0.77% experienced a transient decrease in the visual acuity; both events were mild, resolving without treatment within 10 minutes, and were assessed as unrelated to the treatment
- Two subjects treated with olopatadine 0.77% experienced mild dysgeusia, and both were resolved without treatment
- No clinically relevant differences in adverse drug reactions were found between treatment groups

Figure 1. Ocular itching examined at 3, 5, and 7 minutes after CAC for olopatadine 0.77% versus vehicle at onset of action and at 24-hour duration of action. CAC was performed 27 minutes after drug instillation at onset visit.



**P<0.0001. Ocular itching scores were assessed on a 0 to 4 scale with 0.5-unit increments (0 = none and 4 = incapacitating itch); data are presented as least square means. Olopatadine 0.77% refers to the olopatadine HCl 0.77% (equivalent to 0.7% olopatadine free base) treatment group.*

Figure 2. Ocular itching examined at 3, 5, and 7 minutes after CAC for olopatadine 0.77% versus (**A**) olopatadine 0.2% and (**B**) olopatadine 0.1% at 24-hour duration of action.



**P<0.0001; †P<0.05. Ocular itching scores were assessed on a 0 to 4 scale with 0.5-unit increments (0 = none and 4 = incapacitating itch); data are presented as least square means. Olopatadine 0.77% is equivalent to 0.7% olopatadine free base.*

#Results for endpoints outside FDA approved indications for use are not included.

Efficacy and Safety of Olopatadine Hydrochloride 0.77% in Patients with Allergic Conjunctivitis Using a Conjunctival Allergen-Challenge Model

Signs and Symptoms

Adverse Events

Torkildsen et al. *Clin Ophthalmol.* 2015;9:1703-1713[†]

OVERVIEW

STUDY DESIGN
Phase III, multicenter, double-masked, parallel-group, randomized trial using a conjunctival allergen challenge (CAC) model

STUDY PURPOSE
To compare the safety and efficacy of olopatadine hydrochloride ophthalmic solution 0.77% with vehicle or olopatadine 0.2% in patients with allergic conjunctivitis in a CAC clinical study

STUDY SITE(S)
United States

PATIENTS
Two hundred and two (202) subjects with a history of seasonal or perennial allergic conjunctivitis; mean age across 3 treatment groups 40.7 to 41.2 years (total range: 18 to 77 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2%
Olopatadine hydrochloride ophthalmic solution 0.2% and 0.7% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Allergic conjunctivitis-associated signs and symptoms (ocular itching, conjunctival redness, total redness, chemosis, and tearing scores) at onset of action (3, 5, and 7 minutes postchallenge for itching, 7, 15, and 20 minutes for other variables) and 16- and 24-hour duration of action; adverse events and ocular safety parameters

ANALYSIS AND CONCLUSIONS

Olopatadine 0.77% rapidly provided ocular allergy itch relief that lasted up to 24 hours.

Compared to olopatadine 0.2%, olopatadine 0.7% provided statistically significantly greater ocular allergy itch relief after 24 hours, but the difference was not clinically relevant.

[†]Abhijit Narvekar (clinical trial manager) is an employee of Alcon Research.

STUDY RESULTS[#]

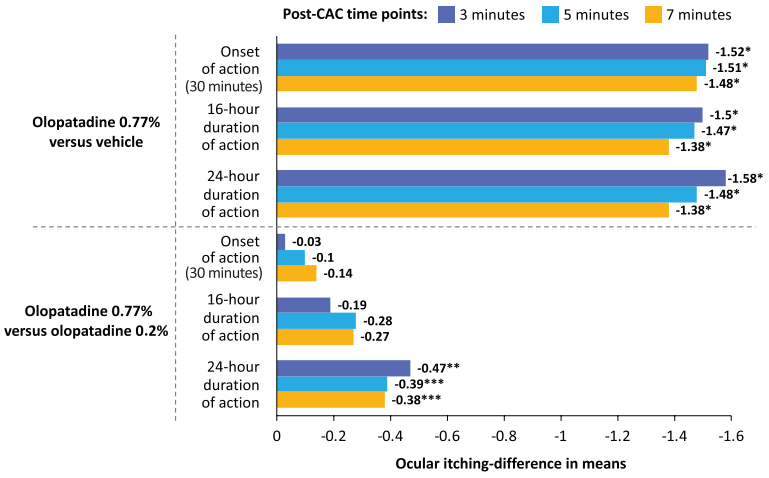
SIGNS AND SYMPTOMS

- Olopatadine 0.77% was superior (P<0.001) to vehicle for treatment of ocular itching at 3, 5, and 7 minutes postchallenge at onset of action and 16- and 24-hour duration of action (P<0.001 for all) (**Figure 1**)
  - Differences in itching were considered clinically relevant (difference of 1 unit or greater from vehicle) for olopatadine 0.77% at all post-CAC time points for onset of action and 16- and 24-hour duration of action
- At 24 hours, olopatadine 0.77% was statistically significantly better than olopatadine 0.2% at all three postchallenge time points for ocular itching (P<0.05) but the difference was not clinically relevant (**Figure 1**)

ADVERSE EVENTS

- No safety concerns were identified for olopatadine 0.77% or 0.2% based on a review of incidence and individual characteristics (onset, intensity, duration, and outcome) of treatment-emergent AEs

Figure 1. Treatment differences in means after conjunctival allergen-challenge (CAC): primary endpoint of ocular itching at onset (27 minutes) and at 16- and 24-hours.



*P<0.001; **P<0.01; ***P<0.05.

[#]*Results for endpoints outside FDA approved indications for use are not included.*

Pooled Analysis of Two Studies Evaluating Efficacy and Safety of Olopatadine Hydrochloride 0.77% in Patients With Allergic Conjunctivitis

Signs and Symptoms

Adverse Events

McLaurin et al. *Clin Ophthalmol.* 2017;11:1089-1097

OVERVIEW

STUDY DESIGN
Pooled data from two phase 3, randomized, multicenter, double-masked, active- and vehicle-controlled conjunctival allergen challenge (CAC) studies

STUDY PURPOSE
To evaluate the integrated efficacy and safety of olopatadine hydrochloride ophthalmic solution 0.77% from a larger dataset by pooling data from the two individual CAC studies

STUDY SITE(S)
United States

PATIENTS
Four hundred forty-eight (448) patients with a history of seasonal or perennial allergic conjunctivitis for at least 1 year; mean age across 3 treatment groups: 39.7 to 41.7 years

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2% and 0.7% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Primary: ocular itching scores for olopatadine 0.77% vs. vehicle at onset and 24 hours), olopatadine 0.77% vs olopatadine 0.2% at 24 hours; Additional: conjunctival redness, total redness, and proportion of itching responders at onset and 24-hour duration of CAC

ANALYSIS AND CONCLUSIONS

This pooled analysis reinforces findings from the two individual CAC studies demonstrating superiority of olopatadine 0.77% over vehicle in reducing ocular allergy itch.

The rapid onset and prolonged duration of action (at least 24 hours) of olopatadine 0.77% further support its once-daily dosing to relieve ocular allergy itch.

STUDY RESULTS#

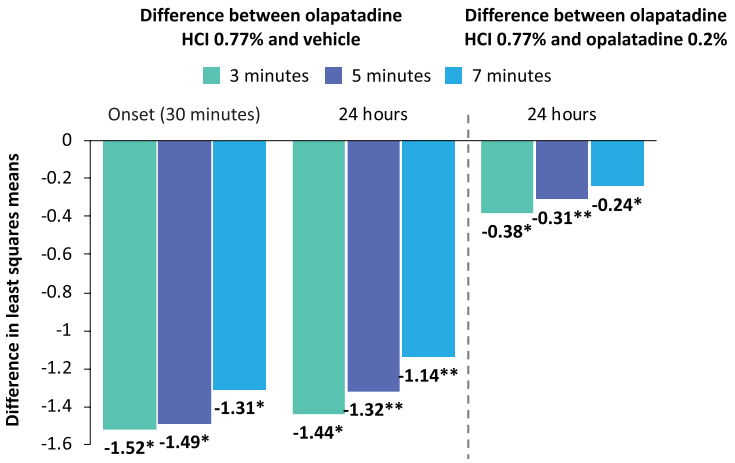
OCULAR ITCHING

- Olopatadine 0.77% was superior to vehicle (P<0.0001) at onset and 24-hour duration of action (difference in means: -1.14 to -1.52) in relieving ocular itch (**Figure 1**)
- Olopatadine 0.77% significantly reduced ocular allergy itch symptoms compared to olopatadine 0.2% (P=0.0009) but this was not clinically relevant

ADVERSE EVENTS

- Five patients discontinued the study due to treatment emergent adverse events (TEAE); however, none of the TEAEs were serious or related to the study treatment
- A review of adverse events did not show any safety concerns with olopatadine 0.77% compared with vehicle and olopatadine 0.2%

Figure 1. Ocular itching: treatment differences in least squares means at onset and 24 hours post-CAC



*CAC, conjunctival antigen challenge. *P<0.0001 overall and at all time points versus vehicle; **P<0.05 versus olopatadine 0.2%.*

#*Results for endpoints outside FDA approved indications for use are not included.*

Pharmacokinetics and Safety of Olopatadine Hydrochloride 0.77% in Healthy Subjects With Asymptomatic Eyes: Data From 2 Independent Clinical Studies

Pharmacokinetics

Adverse Events

Meier et al. *Clin Ophthalmol.* 2017;11:669-681

OVERVIEW

STUDY DESIGN

Phase 1, multicenter, randomized, vehicle-controlled study; Phase 3, multicenter, randomized, vehicle-controlled study

STUDY PURPOSE

To assess the pharmacokinetics (PK) and safety of olopatadine hydrochloride ophthalmic solution 0.77% olopatadine from two independent (Phase 1 and Phase 3, respectively) clinical studies in healthy subjects

STUDY SITE(S)

Single center in the United States

PATIENTS

Phase 1 PK study: 36 healthy subjects (mean age of 42.0 years in olopatadine 0.77% group, 42.8 years in the vehicle group); Phase 3 safety study: 499 healthy subjects (mean age of 32.4 years in the olopatadine 0.77% group, 31.5 years in the vehicle group)

STUDY AGENTS

Olopatadine hydrochloride ophthalmic solution 0.7% (Alcon Vision, LLC)

KEY ENDPOINT(S)

Phase 1: single- and multiple-dose PK parameters such as peak plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}); Phase 3: safety variables such as adverse events (AEs), best-corrected visual acuity (BCVA) and ocular signs

ANALYSIS AND CONCLUSIONS

The Phase 1 PK study demonstrated that olopatadine 0.77% after topical ocular administration of single and multiple doses had a low systemic exposure with quick clearance.

The Phase 3 safety study found that olopatadine 0.77% was well tolerated with no new safety issues after once-daily topical ocular dosing for 6 weeks in adults and in pediatric subjects as young as 2 years of age.

STUDY RESULTS

PHARMACOKINETIC DATA

- Olopatadine 0.77% was absorbed slowly and reached a C_{max} of 1.65 ng/mL following single-dose and 1.45 ng/mL following multiple-dose exposures in 2 hours (T_{max})
- After reaching peak concentrations, olopatadine showed mono-exponential decay following single and multiple doses with similar mean elimination half-life ranging from 2.90 to 3.40 hours (**Figure 1A**)
- No accumulation in olopatadine exposure (C_{max} and area under the plasma concentration-time curve from 0 to 12 hours [AUC_{0-12}]) was evident after multiple doses when compared to a single dose (**Figure 1B**)
- Maximum trough plasma concentration of olopatadine observed over the duration of treatment ranged from 0.108 to 0.247 ng/mL

SAFETY OUTCOMES

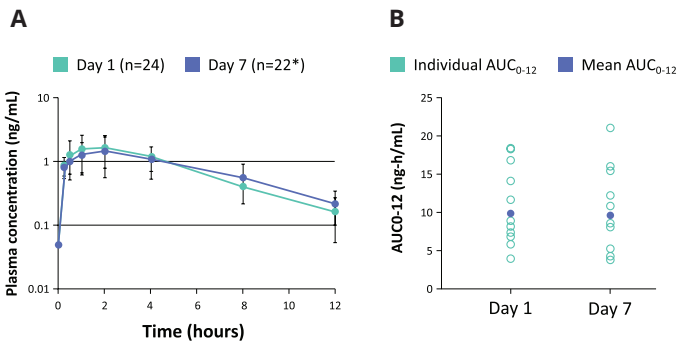
- In the safety study, treatment-emergent adverse events (TEAEs) were reported in 26.7% and 31.4% of subjects with olopatadine 0.77% and vehicle, respectively (**Table 1**)
- Blurred vision was the most frequent ocular TEAE in both treatment groups (olopatadine 0.77% vs vehicle, 4.8% vs 4.1%)
- No deaths or serious adverse events were reported during the study
- No discernible trends in either treatment group were observed for loss of BCVA or safety concerns for any ocular sign parameter, nor were any clinically relevant differences noted for changes in intraocular pressure

Table 1. Summary of TEAEs regardless of study drug relationship by treatment (safety population).

AEs (MedDRA PT), n (%)	Olopatadine 0.77% (n=330)	Vehicle (n=169)
At least 1 TEAE, total	**88 (26.7)**	**53 (31.4)**
Most frequent TEAEs, ≥1%		
Ocular AEs		
Vision blurred	16 (4.8)	7 (4.1)
Dry eye	11 (3.3)	5 (3.0)
Abnormal sensation in the eye	7 (2.1)	7 (4.1)
Corneal staining*	8 (2.4)	7 (4.1)
Conjunctival staining*	6 (1.8)	1 (0.6)
Eye pruritus	5 (1.5)	2 (1.2)
Eye irritation	1 (0.3)	5 (3.0)
Conjunctival hemorrhage	0	2 (1.2)
Non-ocular AEs		
Diarrhea	0	2 (1.2)
Headache	5 (1.5)	3 (1.8)
Dysgeusia	8 (2.4)	0
Upper respiratory tract infection	6 (1.8)	3 (1.8)
Nasopharyngitis	6 (1.8)	3 (1.8)
Gastroenteritis viral	0	2 (1.2)
Ligament sprain	1 (0.3)	2 (1.2)
Cough	1 (0.3)	2 (1.2)

**All of the adverse drug reactions of corneal staining and conjunctival staining were reported by one investigator who conducted fluorescein staining at some post-dose visits. Fluorescein staining was not a protocol required procedure and was not conducted at baseline (screening visits) for any subjects. Olopatadine 0.77%, olopatadine hydrochloride solution 0.77%; vehicle, olopatadine hydrochloride solution 0.77% vehicle. AE, adverse event; MedDRA, medical dictionary for the regulatory activities; PT, preferred term; TEAE, treatment-emergent adverse event.*

Figure 1. Mean olopatadine 0.77% plasma concentration over time (**A**) and AUC_{0-12} (**B**) following single-dose (Day 1) and multiple-dose (Day 7) exposure. single-dose (Day 1) and multiple-dose (Day 7) exposure.



#n=9 at 8- and 12-hour time points due to study consent withdrawal. Data for Day 7 AUC_{0-12} are from 19 subjects. AUC_{0-12}, area under the plasma concentration–time curve from 0 to 12 hours.

Projected 24-Hour Post-Dose Ocular Itching Scores Post-Treatment with Olopatadine 0.7% Versus 0.2%

Fidler et al. *J Pharmacokinet Pharmacodyn.* 2018;45:593-605*

OVERVIEW

STUDY DESIGN
Differential odds model using data from two conjunctival allergen challenge (CAC) studies to characterize individual-level and population-level response to ocular itching following olopatadine treatment; data analyzed retrospectively

STUDY PURPOSE
To characterize patients who have better itching relief at 24 hours when taking olopatadine hydrochloride ophthalmic solution 0.7% treatment instead of olopatadine 0.2% (in terms of proportions of responses) and relate this to the severity of baseline itching as an indirect metric of a patient's sensitivity to antihistamines

STUDY SITE(S)
United States

PATIENTS
Five hundred forty-seven (547) patients with a history of allergic conjunctivitis, including 10,759 itching observations from two CAC studies; mean age 40.9 years (range: (18.0 to 77.0 years)

STUDY AGENTS
Olopatadine hydrochloride ophthalmic solution 0.2%
Olopatadine hydrochloride ophthalmic solution 0.2% and 0.7% (Alcon Vision, LLC)

KEY ENDPOINT(S)
Prediction of 24-hour ocular itching scores and quantification of differences in 24-hour itching relief after treatment (including impact of baseline itching severity, vehicle effect and the drug effect)

ANALYSIS AND CONCLUSIONS

A differential odds model predicted that a higher proportion of patients who received olopatadine 0.7% would experience itching relief within 24 hours of treatment compared with patients who received olopatadine 0.2%, and this prediction was confirmed by retrospective clinical analysis

Overall, the number of allergy patients who achieved itching relief with olopatadine 0.7% increased with higher baseline itching severity scores, when compared to olopatadine 0.2% patients.

*Matthew Fidler, Abayomi Ogundele, and David Covert are Novartis employees. Ramesh Sarangapani is an Alcon employee.

STUDY RESULTS

MODELING ANALYSIS

- Observed proportions and simulations of treatment and the various time points of CAC in the modeling analysis are shown in **Figure 1**
- Overall, population predictions were less precise than the individual predictions, and vehicle/baseline predictions were more precise than predictions in the presence of olopatadine
- There was also a slight underprediction of the ability of the 0.7% doses to produce no itching at any time point, but more especially at the later time points; however, other scores seemed to be predicted fairly well

COMPARISONS BETWEEN 0.2% AND 0.7% OLOPATADINE

- With increasing baseline severity, the percentage of population with relief at 24 hours after olopatadine 0.7% was higher than that after olopatadine 0.2% (from 5 to 14% more relief)
- Overall, these data were suggestive of improved efficacy of the higher 0.7% dose in more severe patients than what would be observed in the 0.2% dose
- In the larger simulated population, the mean difference in 24-hour allergy relief showed that olopatadine 0.7% provided itching relief in an additional 10% of the population whose itching could not be controlled with olopatadine 0.2%
- As baseline itching scores increased, approximately 25% of the population who could not be relieved with olopatadine 0.2% had itching relief with olopatadine 0.7%
- This increasing effectiveness of olopatadine was so substantial that the dose effect was included as a significant covariate of the model, implying that there was an increased effect not explained by simply increasing the dose

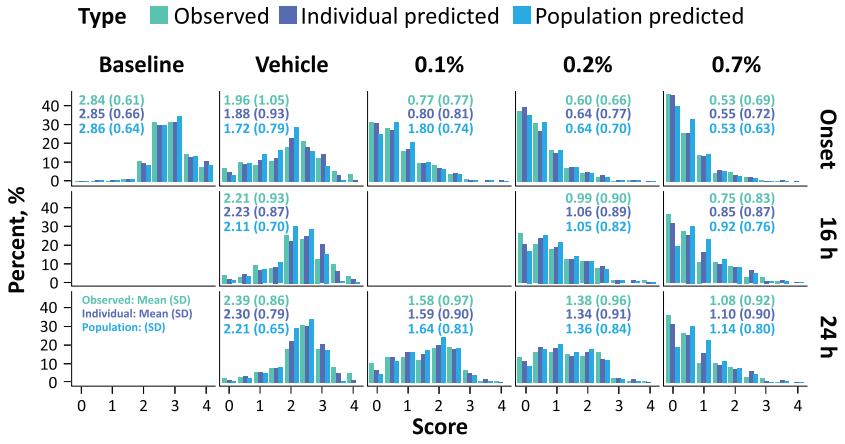


Figure 1. Histogram of observed, individual predicted, and population predicted itching score frequencies, stratified by treatment and nominal time point, showing simulation of treatment (baseline, vehicle, 0.1, 0.2 and 0.7%) and the time points of CAC (onset, 16 h, and 24 h).

Each category's simulated itching proportion is graphically compared to the observed itching proportions. Additionally, the plot is annotated with the mean (SD) for the itching scores under the simulation conditions and observed between the pooled clinical studies.

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