

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

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ABSTRACT

Background: Seasonal allergic conjunctivitis (SAC) is caused by seasonal allergens and usually manifests as ocular itching and bulbar conjunctival injection (redness). Treatment options for SAC include corticosteroids and dual-acting antihistamine and mast-cell stabilizers.

Objective: Our objective was to compare the efficacy and tolerability of loteprednol etabonate (LE), a C-20 ester-based corticosteroid, with those of olopatadine, a dual-acting antihistamine mast-cell stabilizer, in Chinese patients.

Methods: This was a multicenter, randomized, investigator-masked, parallel group study. Patients with acute SAC experiencing grade 4 ocular itching and grade 2 or higher bulbar conjunctival injection received either LE suspension 0.2% QID at 4-hour intervals or olopatadine solution 0.1% BID at 6- to 8-hour intervals bilaterally for 15 days. Primary efficacy end points included the change from baseline (CFB) in ocular itching and bulbar conjunctival injection at day 15. The primary analysis tested the noninferiority of LE suspension 0.2% to olopatadine solution 0.1%. Tolerability outcomes included the incidence of adverse events (AEs), biomicroscopy findings, visual acuity, and intraocular pressure.

Results: A total of 300 patients were randomly assigned, and 293 were included in the per-protocol population (LE, n = 147; olopatadine, n = 146). Mean (SD)

CFB at day 15 in the LE and olopatadine treatment groups, respectively, was -3.74 (0.47) and -3.28 (0.91) for ocular itching and -1.91 (0.52) and -1.71 (0.59) for bulbar conjunctival injection. The 95% CI for the differences in CFB in ocular itching (-0.59 to -0.27) and bulbar conjunctival injection (-0.27 to -0.08) was less than the prespecified noninferiority limit of 0.3. Treatment differences in CFB were significantly better with LE compared with olopatadine for both end points ($P \leq 0.0006$). Ocular AEs were few and similar between treatment groups. There were no clinically significant biomicroscopy or visual acuity findings, and no patient experienced a clinically significant increase in intraocular pressure (≥ 10 mm Hg).

Conclusion: Results of this investigator-masked study with Chinese patients suggest LE suspension 0.2% was noninferior to olopatadine solution 0.1% for the treatment of SAC. Both LE suspension 0.2% and olopatadine solution 0.1% were well tolerated. [ClinicalTrials.gov](http://dx.doi.org/10.1016/j.clinthera.2012.04.024) identifier: NCT01435460. (*Clin Ther.* 2012;xx:xxx) © 2012 Elsevier HS Journals, Inc. All rights reserved.

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Key words: allergic conjunctivitis, antihistamines, corticosteroids, loteprednol etabonate, mast-cell stabilizers, olopatadine.

INTRODUCTION

The conjunctiva, or mucous membrane component of the ocular surface, is continually exposed to a variety of airborne antigens¹ that can lead to inflammation, often termed *allergic conjunctivitis*. The incidence of allergic conjunctivitis varies from 15% to 40% in the population.^{2–4} Based on the presentation, allergic conjunctivitis can be classified as seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis, vernal keratoconjunctivitis, or giant papillary conjunctivitis.⁵ The most frequently encountered of these are SAC and PAC, with >95% of the ocular allergy cases being classified as one of these conditions.⁶ Although SAC is usually an acute or subacute manifestation characterized by peaks of signs and symptoms such as ocular itching, dryness, burning, redness, and pain, patients with PAC can experience these symptoms year round.⁷

Topical antihistamine mast-cell stabilizers and corticosteroids are both effective in treating symptoms associated with allergic conjunctivitis, but they differ in their mechanisms of action. Antihistamine mast-cell stabilizers work by competitively blocking histamine binding to H₁ receptors and inhibiting mast-cell degranulation. Corticosteroids work at the molecular and cellular level; they bind with receptors and stimulate the synthesis of those proteins that regulate multiple aspects of the anti-inflammatory response, as well as modulate the mast-cell response by inhibiting mediators that induce mast-cell proliferation and recruitment.⁷ They also increase histaminase stores, thereby reducing levels of available histamine, and down-regulate expression of histamine receptors.^{8–10} However, their use has been limited due to concerns about unwanted side effects, such as increased intraocular pressure (IOP), cataract formation, and vulnerability to infection.⁵

Olopatadine hydrochloride is a dual-acting selective histamine H₁ receptor antagonist and mast-cell stabilizer,^{11–13} and loteprednol etabonate (LE) is a C-20 ester corticosteroid. LE differs from other corticosteroids in that the C-20 ketone position of the traditional prednisolone structure is replaced by an ester. After exerting its effects, LE is rapidly converted into an in-

active metabolite.¹⁴ This, in turn, results in fewer IOP elevations compared with older corticosteroids.^{15,16} In addition, the lack of a ketone at the C-20 position precludes formation of Schiff base intermediates with lens protein, considered a first step in cataractogenesis.¹⁷ Both olopatadine hydrochloride ophthalmic solution 0.1%* and LE ophthalmic suspension 0.2%† have been reported to be effective and well tolerated in randomized controlled studies in SAC.^{18–22}

Our study evaluated the efficacy and tolerability of LE suspension 0.2% compared with olopatadine hydrochloride solution 0.1% for the temporary relief of signs and symptoms of SAC in a population of Chinese patients. In addition to providing comparative efficacy for 2 distinct classes of drugs used in the treatment of patients with SAC, our study was also conducted, in part, to meet regulatory requirements for registration of LE suspension 0.2% in China.

METHODS

Study Design

This randomized, single-masked, active-controlled, parallel group study (ClinicalTrials.gov identifier: NCT 01435460) included 7 clinical centers in China. Patients with SAC were enrolled from August 2010 through April 2011. All patients randomly assigned were Chinese. The study was conducted in accordance with Good Clinical Practice as described in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice 1996, China State Food and Drug Administration's Good Clinical Practices, applicable local regulations, and the Declaration of Helsinki.^{23–25} The protocol was approved by the Medical Ethics Committees of the Eye Nose and Throat Hospital of Fudan University and the First Affiliated Hospital of Medical School of Zhejiang University. All patients provided written informed consent at screening (see Supplemental Figure in the online version at <http://dx.doi.org/10.1016/j.clinthera.2012.04.024>).

Included in this study were patients aged 18 years or older who were diagnosed with acute SAC with grade 4 (severe) ocular itching and grade 2 or higher (ie, moderate to severe) bulbar conjunctival injection (red-

*Trademark: Patanol® (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

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ness) in each eye at the first study visit (visit 1). Female patients of childbearing age were included only if a negative urine pregnancy test was observed at the first study visit. Patients participating in any drug or device clinical investigation within 30 days before entry into this study or during the period of study participation, female patients who were breastfeeding, and patients who were not using an approved method of birth control during the study duration were excluded from the study. Also excluded were patients using any of the following drugs 7 days before the first study visit: systemic or ocular H_1 antihistamines; H_1 antihistamine-vasoconstrictor drug combinations; decongestants; monoamine oxidase inhibitors; other topical ophthalmic preparations; prostaglandins or prostaglandin derivatives; and ocular, topical, or systemic NSAIDs. Patients using inhaled, ocular, or topical corticosteroids or mast-cell stabilizers for 14 days, depo-corticosteroids for 45 days, and immunosuppressive agents for 2 months, respectively, before the first study visit were also excluded. Finally, patients who had a known hypersensitivity to the study medications or their components (including benzalkonium chloride) or contraindications to ocular corticosteroids, an intraocular pressure ≥ 21 mm Hg in either eye or any type of glaucoma, best-corrected distance visual acuity (E Chart decimal) of ≤ 0.5 in either eye, a history of any severe or serious ocular pathology or medical conditions, and those patients unable or unwilling to discontinue wearing contact lenses during the study were also excluded.

Study Treatments and Assessments

Eligible patients were stratified by site and randomly assigned in a 1:1 ratio by a computer-generated randomization list to investigator-masked treatment with either LE suspension 0.2% or olopatadine solution 0.1%. Patients randomly assigned were instructed to self-administer 1 drop of LE suspension 0.2% QID at approximately 4-hour intervals (LE suspension group) or 1 drop of olopatadine solution 0.1% BID at intervals of 6 to 8 hours or more (olopatadine solution group), in both eyes for 15 days and to record each study medication instillation in a patient diary. The randomization list was developed before enrollment by an independent statistician using a computer random-number generator to select random blocks of 6 kit boxes. Uniquely numbered and randomly assigned patient kit boxes were provided to the investigator at each site and assigned to each patient in ascending order.

For purposes of masking, labels on the commercial bottles of LE suspension 0.2% and olopatadine solution 0.1% were replaced with investigational labels and bottles were packaged in identical kit boxes in an attempt to mask patients. However, due to differences in the appearance of the bottles, patients were not fully masked. To ensure investigators were masked, a masked designee at each site dispensed the kit boxes to patients according to the randomization list and retrieved them from patients at the end of the study; investigators were not present during study treatment dispensation to and retrieval from patients. Unmasked designees also instructed patients on proper instillation of study medication.

Patients completed 3 study visits. At visit 1, on the first day of the study, informed consent, demographic data, and relevant medical and ocular history was collected. Baseline ocular data for signs and symptoms was collected and, if applicable, a urine pregnancy test was conducted on this day. Patient diaries, used to assess study treatment exposure and treatment compliance only, and patient medication kits were provided. Visit 2 was conducted on day 8 (± 1 day) and visit 3 on day 15 (± 2 days). Data on concomitant medications, visual acuity (VA), ocular symptoms and signs, IOP, and adverse events (AEs) was collected at all study visits. Patient diaries were reviewed on day 8 and day 15, and collected on day 15, along with medication kits, after the final study dose was instilled. Overall study compliance was calculated by dividing the total number of doses recorded in the study diary for a patient for the entire treatment period by the number of expected dosings and then multiplying by 100%.

Outcomes Measures

The investigator assessed ocular signs and symptoms at baseline and each study visit thereafter. Ocular signs included bulbar conjunctival injection, palpebral conjunctival injection, chemosis, and eyelid erythema. These were evaluated using a slit-lamp biomicroscope and graded on a 0 to 3 scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). Ocular symptoms included ocular itching, discomfort, foreign-body sensation, burning/stinging, photophobia, tearing, and discharge. Ocular symptoms were graded on a 0 to 4 scale (0 = absent, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe) and assessed by the investigator through direct patient inquiry. All efficacy variables were evaluated for both eyes at each visit.

The dual primary efficacy end points were change from baseline (CFB) to day 15 (visit 3) in ocular itching and bulbar conjunctival injection. Secondary efficacy end points included the CFB in ocular itching and bulbar injection severity at day 8 (visit 2) and the CFB at each visit in other signs (ie, palpebral injection, chemosis, and erythema) and symptoms (ie, discomfort, foreign-body sensation, burning/stinging, photophobia, tearing, and discharge).

Tolerability assessments were based on AEs, VA, biomicroscopy, and IOP measurements. AEs were collected through patient query or observation. The incidence and type of AEs reported by the patient or observed by the investigator at each study visit were collected from the time informed consent was obtained until the study exit. VA was measured at all visits using standardized E charts. The same VA testing method was used for all study visits for each patient. Biomicroscopy parameters were evaluated at each visit using a 0 to 3 grading scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). A calibrated noncontact tonometer was used to measure IOP. Clinically significant IOP increases were defined as ≥ 10 mm Hg from baseline.

Statistical Methods

Approximately 296 patients were planned to be randomly assigned to yield approximately 125 patients in each treatment group completing the study without major protocol deviations. The final sample size assumed a 15% dropout or major protocol deviation rate, based on previous studies of LE in SAC.^{20,21} This sample size would yield >85% power to show noninferiority with a 1-sided, $\alpha = 0.025$ test of LE suspension to olopatadine solution in the CFB of ocular itching and bulbar conjunctival injection severity, assuming a common SD of 0.775 in CFB. This sample size was based on a noninferiority limit of 0.30 in both end points.

Primary efficacy end-point analyses were performed on the per-protocol (PP) population. ANCOVA was conducted to estimate treatment mean differences and their corresponding 2-sided 95% CI and *P* value were used to compare treatment groups in the noninferiority setting. The ANCOVA models included terms of treatment, site, and baseline of the variable. Treatment-by-baseline and treatment-by-site interactions were included if found to be significant ($P < 0.1$). No adjustments for multiple primary end points were

made, as the order in which the hypothesis was tested was fixed and sequentially prespecified (ie, ocular itching was analyzed first, followed by bulbar conjunctival injection).²⁶ Noninferiority was concluded if the upper limit of the 2-sided 95% confidence limits for both end points was ≤ 0.3 . Supportive analysis of the primary efficacy end points was conducted on the intent-to-treat (ITT) population using the same ANCOVA model. In both the primary analysis and supportive analysis, missing day 15 observations were imputed for patients that were placed on rescue therapy or discontinued the study due to failure to show improvement using the last observation carried forward. The secondary efficacy analyses also used the same ANCOVA model specified for the primary analysis. Supportive repeated measures analyses with unstructured covariance matrices were performed to evaluate ocular itching and bulbar conjunctival injection mean CFB over time.²⁷ Differences in the proportion of patients with complete resolution of ocular itching and bulbar conjunctival injection at day 15 were evaluated post hoc using Fisher's exact test.

Safety profiles were assessed by evaluating all reported AEs, change in VA, and IOP. Continuous variables (ie, VA and IOP) were analyzed using an ANCOVA model similar to that used for the primary end points. Treatment differences in the incidence of AEs were tested using Fisher's exact test.

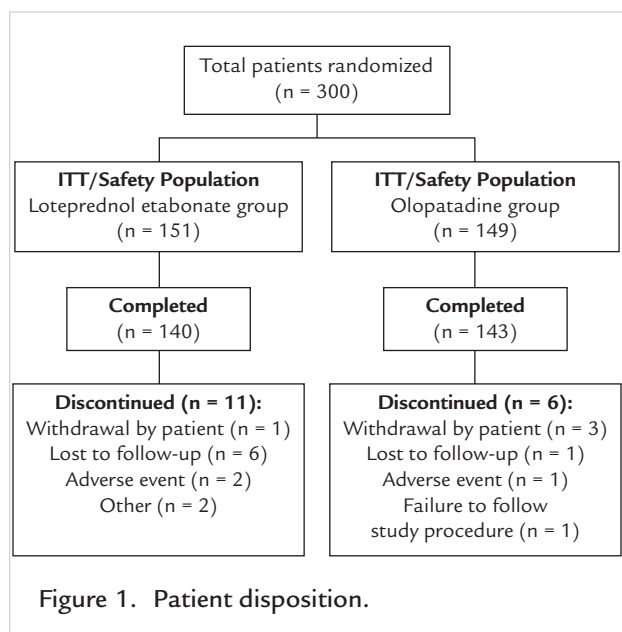
The ITT population included all patients who were randomly assigned. The PP population included all patients in the ITT population with no protocol deviation that was in any way likely to seriously affect the primary outcomes of the study. The safety population was defined as all patients who received at least 1 dose of study medication and for whom safety data were available, and was used for the safety analyses.

All statistical analyses were conducted using SAS version 9.1 or higher (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Patient Disposition

A total of 300 patients were randomly assigned to receive LE suspension ($n = 151$) or olopatadine solution ($n = 149$) and were included in both the ITT population and safety population. Seven patients were excluded from the PP population due to major protocol deviations, including noncompliance with study visit (1 patient in each group), noncompliance with



eligibility criteria (LE suspension, $n = 2$; olopatadine solution, $n = 1$), noncompliance with study treatment (LE suspension, $n = 1$), and unauthorized concomitant therapy (olopatadine solution, $n = 1$); leaving 293 patients in the PP population (LE suspension, $n = 147$; olopatadine solution, $n = 146$). A total of 283 patients (94.3%) completed the study (140 patients [92.7%] for the LE suspension group and 143 patients [96.0%] for the olopatadine solution group). Reasons for discontinuation included loss to follow-up (LE suspension, $n = 6$; olopatadine solution, $n = 1$), withdrawal of consent (LE suspension, $n = 1$; olopatadine solution, $n = 3$), AE (LE suspension, $n = 2$; olopatadine solution, $n = 1$), failure to follow study procedure (olopatadine solution, $n = 1$), and other (LE suspension, $n = 2$). Details of patient disposition are provided in Figure 1.

Patient Baseline Characteristics

The demographic characteristics of patients in the LE suspension and olopatadine solution groups were similar (Table I). All randomly assigned patients were Chinese, with a mean age of 40.6 years. Mean (SD) baseline ocular itching and bulbar injection severity was comparable between treatment groups; mean (SD) baseline ocular itching severity was 4.00 (0.000) for both groups and mean (SD) baseline bulbar conjunctival injection was 2.13 (0.328) and 2.12 (0.300) for the LE suspension and olopatadine solution groups, re-

spectively. Mean decimal VA for right and left eyes was 1.02 and 1.01 in the LE suspension group and 1.02 and 1.02 in the olopatadine solution group. Baseline IOPs ranged from 7.6 mm Hg and 21.0 mm Hg.

Based on patient diaries, the mean (SD) days on study treatment was 14.7 (2.11) and 15.0 (1.55) in the LE suspension and olopatadine solution groups, respectively, and the mean (SD) number of dosages per eye was 110.3 (18.8) and 58.2 (6.5) in the LE suspension and olopatadine solution groups, respectively. The mean (SD) treatment compliance rate was 93.6% (7.5) and 97.1% (2.6) for the LE suspension and olopatadine solution groups, respectively.

Efficacy

Primary Efficacy End Points: Day 15 (Visit 3) Change From Baseline in Ocular Itching and Bulbar Conjunctival Injection

Day 15 mean (SD) ocular itching severity was 0.26 (0.47) and 0.72 (0.91) in the LE and olopatadine solution groups, respectively, and day 15 mean (SD) bulbar injection severity was 0.23 (0.46) and 0.40 (0.54), respectively. Table II presents the change from baseline to day 15 in ocular itching and bulbar injection severity for the PP population and Figures 2 and 3 present longitudinal plots of the mean CFB for these end points. Mean (SD) CFB at day 15 in the LE suspension and olopatadine solution groups, respectively, was -3.74 (0.47) and -3.28 (0.91) for ocular itching ($P < 0.0001$) and -1.91 (0.52) and -1.71 (0.59) for bulbar conjunctival injection ($P = 0.0006$). The upper limits of the 95% CIs for both end points were less than the prespecified noninferiority margin of 0.30, indicating noninferiority of LE to olopatadine for these end points. Analysis of noninferiority was also conducted in the ITT population, and results of that analysis were consistent with that obtained in the PP population (data not shown). As was the case with the PP population, the difference in mean CFB was statistically significant in favor of LE suspension ($P \leq 0.0004$).

The proportion of patients with complete resolution of ocular itching and bulbar conjunctival injection at day 15 is presented in Figure 4. The proportion of patients with complete resolution of ocular itching was 74.6% (103 of 138) and 50.7% (72 of 142) in the LE suspension and olopatadine solution groups, respectively, and the proportion of patients with complete resolution of bulbar conjunctival injection was 78.3% (108 of 138) and 61.3% (87 of 142), respectively, with

Table I. Demographic data (intent-to-treat population).

	Loteprednol Etabonate Suspension 0.2%* (n = 151)	Olopatadine Hydrochloride Solution 0.1%† (n = 149)	Total (n = 300)
Age, mean (SD), y	40.5 (14.01)	40.6 (12.85)	40.6 (13.43)
Sex, no. (%)			
Male	52 (34.4)	46 (30.9)	98 (32.7)
Female	99 (65.6)	103 (69.1)	202 (67.3)
Chinese race, no. (%)	151 (100.0)	149 (100.0)	300 (100.0)
Current medical and ocular history, no. (%)			
Conjunctivitis allergic	151 (100.0)	149 (100.0)	300 (100.0)
Duration of disease			
<6 mos	39 (25.8)	38 (25.5)	77 (25.7)
>6 mos	112 (74.2)	111 (74.5)	223 (74.3)
Cataract	1 (0.7)	1 (0.7)	2 (0.7)
Current medical and nonocular history, no. (%)			
Immune system disorders			
Rhinitis seasonal	4 (2.6)	4 (2.7)	8 (2.7)
Rhinitis allergic	4 (2.6)	0	4 (1.3)
Asthma	1 (0.7)	0	1 (0.3)

*Trademark: Alrex® (Bausch + Lomb, Rochester, New York).

†Trademark: Patanol® (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

both outcomes significantly better with LE suspension compared with olopatadine solution ($P \leq 0.00269$).

Secondary Efficacy End Points

Day 8 mean (SD) ocular itching severity was 1.54 (0.876) and 1.98 (0.851) in the LE and olopatadine solution groups, respectively, and day 8 mean (SD) bulbar injection severity was 0.78 (0.612) and 0.94 (0.587), respectively. At day 8, the mean (SD) CFB in ocular itching was -2.46 (0.876) and -2.02 (0.851), for the LE suspension and olopatadine solution groups, respectively ($P < 0.0001$), and the mean (SD) CFB in bulbar injection was -1.36 (0.569) and -1.18 (0.610), respectively ($P = 0.0029$). As was the case for these outcomes at day 15, supportive analyses for the ITT population were consistent with those obtained with the PP population (data not shown) and the difference in mean CFB was also statistically significant in favor of LE suspension ($P \leq 0.0017$).

Table III shows a summary of the change from baseline to days 8 and 15 in other ocular signs (ie, palpebral injection, chemosis, and erythema) and symptoms (ie, discomfort, foreign-body sensation, burning/stinging, photophobia, tearing, and discharge) in the PP population. The differences between treatment groups in mean CFB to day 8 and day 15 for other signs and symptoms were either significantly different in favor of LE, or were similar between treatments. All of the upper limits of the 95% CI for mean differences between treatment groups were less than the prespecified non-inferiority margin.

Safety Profile

A total of 5 patients (3.3%) in the LE suspension group and 2 patients (1.3%) in the olopatadine solution group reported ≥ 1 treatment-emergent adverse event (TEAE). Ocular TEAEs were reported by 3 patients (2.0%) in the LE suspension group and 2 pa-

Table II. Change from baseline in ocular itching and bulbar conjunctival injection (per-protocol population).*

	Ocular Itching			Bulbar Conjunctival Injection		
	Treatment		95% CI [§]	Treatment		95% CI [§]
	Loteprednol Etabonate Suspension 0.2% [†]	Olopatadine Solution 0.1% [‡]		Loteprednol Etabonate Suspension 0.2% [†]	Olopatadine Solution 0.1% [‡]	
Day 8 (visit 2)						
No.	140	141		140	141	
Mean (SD)	-2.46 (0.876)	-2.02 (0.851)		-1.36 (0.569)	-1.18 (0.610)	
Mean difference	-0.44 (0.864)		-0.61 to -0.25	-0.18 (0.590)		-0.29 to -0.06
<i>p</i> [§]	<0.0001			0.0029		
Day 15 (visit 3)						
No.	138	142		138	142	
Mean (SD)	-3.74 (0.469)	-3.28 (0.908)		-1.91 (0.521)	-1.71 (0.585)	
Mean difference	-0.46 (0.726)		-0.59 to -0.27	-0.19 (0.554)		-0.27 to -0.08
<i>p</i> [§]	<0.0001			0.0006		

*Range: ocular itching (0–4); bulbar conjunctival injection (0–3). Mean (SD) baseline ocular itching severity was 4.00 (0.000) for both groups and mean (SD) baseline bulbar conjunctival injection was 2.13 (0.328) and 2.12 (0.300) for the loteprednol etabonate suspension and olopatadine solution groups, respectively. Missing data were imputed for patients that were placed on rescue therapy or who discontinued due to treatment failure, using the last observation before discontinuation of study treatment.

[†]Trademark: Alrex[®] (Bausch + Lomb, Rochester, New York).

[‡]Trademark: Patanol[®] (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

[§]Based on the ANCOVA model including treatment and center as fixed factors and baseline score as a covariate. Treatment-by-center and treatment-by-baseline interactions were tested, found to be nonsignificant, and excluded from the final model. 95% CI and *P* values were calculated using least squares mean.

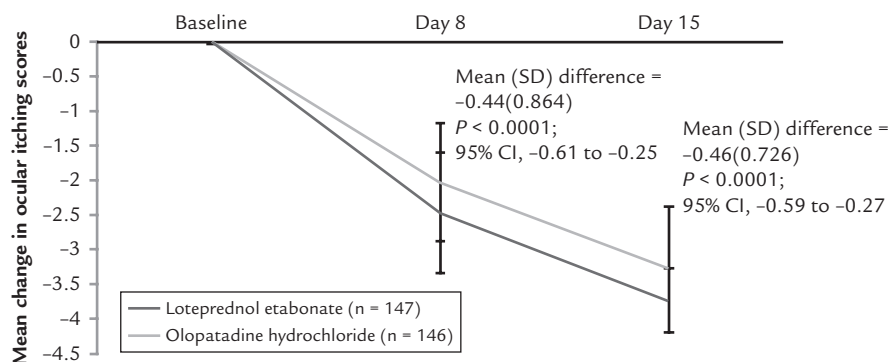


Figure 2. Change in mean ocular itching from baseline at days 8 and 15. Negative values indicate changes in favor of loteprednol etabonate. CI and *P* values were calculated using least squares mean.

tients (1.3%) in the olopatadine solution group (Table IV). Ocular TEAEs reported by patients in the LE suspension group included swollen eyelid ($n = 1$), instillation-site abnormal sensation ($n = 1$), and instillation-site stinging ($n = 1$). These TEAEs were considered either probably or possibly related to study treatment. In the olopatadine solution group, ocular TEAEs reported by patients included epidemic hemorrhagic conjunctivitis ($n = 1$) and blurred vision ($n = 1$), both of which were unrelated to study treatment. A single patient in each group discontinued the study due to an ocular adverse event (LE suspension group, swollen eyelid; olopatadine solution group, epidemic hemorrhagic conjunctivitis). No nonocular TEAEs were reported in the olopatadine solution group and 2 patients (1.3%) in the LE suspension group reported 3 nonocu-

lar TEAEs. These included sinusitis ($n = 1$) and nasal septum deviation ($n = 1$) in 1 patient, and fibula fracture ($n = 1$) in the other patient, all of which were unrelated to study treatment. The nasal septum deviation event was considered a serious AE and that patient was discontinued from the study. All other TEAEs were mild to moderate in severity.

There were no clinically significant VA or biomicroscopy findings in either treatment group. Mean decimal VA was 1.01 to 1.02 for both treatment groups at day 8 and day 15 ($P \geq 0.6577$ at day 15). Among eyes with nonmissing data, ocular signs were absent or mild in the majority ($>95\%$) of eyes by day 15.

Figure 5 presents the mean (SD) IOP changes from baseline at day 8 and day 15 by treatment group for right and left eyes. Differences between treatments in

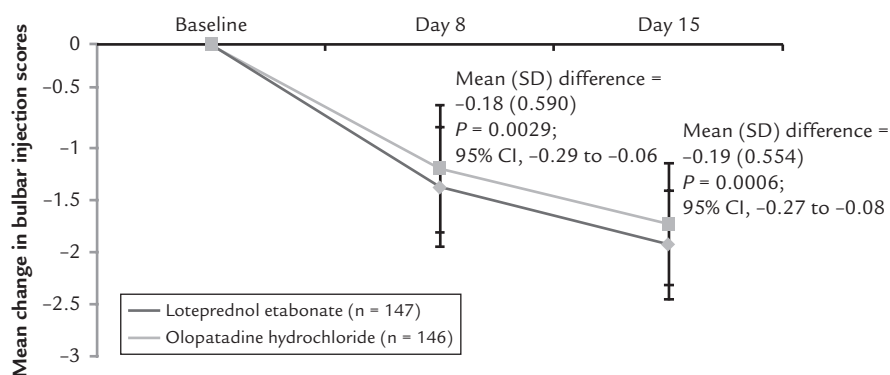


Figure 3. Change in mean bulbar injection from baseline at days 8 and 15. Negative values indicate changes in favor of loteprednol etabonate. CI and *P* values were calculated using least squares mean.

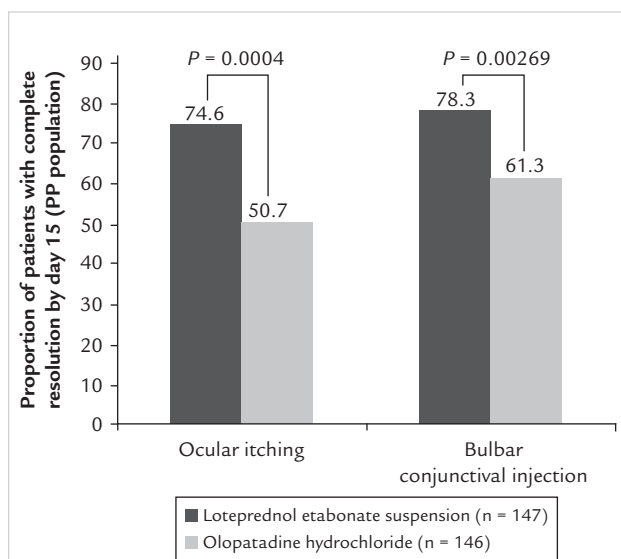


Figure 4. Proportion of patients with complete resolution of ocular itching and bulbar conjunctival injection at day 15.

mean IOP CFB at day 15 were small, 0.50 (2.257) mm Hg and 0.59 (2.150) mm Hg, for right and left eyes, respectively. Although these differences were statistically significant ($P \leq 0.0174$), they are considered clinically nonsignificant.

A total of 9 patients (6.0%) in the LE suspension group and 4 patients (2.7%) in the olopatadine solution group experienced an increase in IOP of >5 mm Hg from baseline, but no patients in either treatment group experienced an increase in IOP of ≥ 10 mm Hg from baseline. Treatment-emergent IOP of ≥ 22 mm Hg was seen in 1 patient in both treatment groups. No patients in either treatment group had a treatment-emergent IOP ≥ 30 mm Hg.

DISCUSSION

SAC is a common condition caused by allergens such as ragweed and various pollens and occurs more frequently during spring and autumn, when the levels of these airborne irritants are high. Allergen exposure causes a type I immunoglobulin E hypersensitivity reaction, culminating in ocular itching, burning, tears, redness, and pain.⁵ Discomfort due to signs and symptoms of SAC can have a considerable impact on quality of life and productivity.⁴ Prophylaxis via avoidance of the causative allergen is desirable, but is not feasible for most patients, particularly those suffering from pollen

allergies. Although symptoms persist throughout the allergy season, they can exacerbate, depending on the extent of exposure to the allergens and the weather.²⁸ In this case, topical ophthalmic agents are the most commonly used treatment option.

The objective of this study was to compare the efficacy and tolerability of LE ophthalmic suspension 0.2%, a C-20 ester-based corticosteroid formulation, with that of olopatadine hydrochloride ophthalmic solution 0.1%, a dual-acting antihistamine mast-cell stabilizer formulation, in Chinese patients. The mean (SD) CFB at day 15 in the LE suspension and olopatadine solution groups, respectively, was -3.74 (0.47) and -3.28 (0.91) for ocular itching, and -1.91 (0.52) and -1.71 (0.59) for bulbar conjunctival injection. Not only did LE suspension meet the noninferiority criteria to olopatadine solution based on the CFB for both ocular itching and bulbar injection at day 15, but treatment with LE suspension was significantly better for both end points ($P \leq 0.0006$). In addition, the 95% CI for ocular itching fell almost entirely outside the noninferiority margin, suggesting the possible superiority of LE compared with olopatadine solution for this end point, although additional studies designed to assess superiority are needed to confirm this finding. Results of secondary end points were consistent with primary outcomes: LE suspension 0.2% met the noninferiority criteria for all additional signs and symptoms assessed.

Both treatments were well tolerated. Ocular AEs were few and similar between treatment groups, and there were no clinically significant biomicroscopy or VA findings in either treatment groups. Although there was a small (<1 mm Hg) difference in CFB in mean IOP in patients treated with LE suspension compared with patients treated with olopatadine solution at day 15, no patients experienced a clinically significant increase in IOP (≥ 10 mm Hg). These results are consistent with findings from previous studies of LE used in the treatment of other ocular inflammatory conditions,^{8,29–32} and a retrospective study of tolerability data from 397 patients treated with LE 0.2% suspension at least once a day for 28 days or longer as a primary or adjunct therapy for PAC or SAC.⁸ There were no clinically meaningful changes in IOP reported. In fact, there were no cases of steroid-induced increase in IOP of ≥ 4 mm Hg.

Results for LE suspension 0.2% observed in the present study are consistent with previous vehicle-con-

Table III. Change from baseline to days 8 and 15 in other ocular signs and symptoms (per-protocol population).*

	CFB to Day 8 (Visit 2)			CFB to Day 15 (Visit 3)		
	Loteprednol Etabonate Suspension 0.2% [†]	Olopatadine Hydrochloride Solution 0.1% [‡]	95% CI [§]	Loteprednol Etabonate Suspension 0.2% [†]	Olopatadine Hydrochloride Solution 0.1% [‡]	95% CI [§]
Palpebral injection						
No.	140	141		138	142	
Mean (SD)	-0.94 (0.585)	-0.84 (0.587)		-1.54 (0.706)	-1.47 (0.770)	
Mean difference (SD)		-0.11 (0.586)	-0.23 to -0.02		-0.07 (0.739)	-0.20 to 0.01
<i>p</i> [§]		0.0171			0.0887	
Chemosis						
No.	140	141		138	142	
Mean (SD)	-0.49 (0.625)	-0.50 (0.556)		-0.57 (0.678)	-0.59 (0.642)	
Mean difference (SD)		-0.01 (0.591)	-0.07 to 0.05		-0.02 (0.660)	-0.02 to 0.01
<i>p</i> [§]		0.6453			0.3876	
Erythema						
No.	140	141		138	142	
Mean (SD)	-0.25 (0.474)	-0.28 (0.479)		-0.33 (0.568)	-0.38 (0.569)	
Mean difference (SD)		0.03 (0.477)	-0.07 to 0.05		0.05 (0.568)	-0.03 to 0.03
<i>p</i> [§]		0.7431			0.9880	
Discomfort						
No.	140	141		138	142	
Mean (SD)	-0.98 (0.726)	-0.81 (0.701)		-1.51 (0.801)	-1.23 (0.872)	
Mean difference (SD)		-0.17 (0.713)	-0.26 to -0.03		-0.28 (0.838)	-0.34 to -0.14
<i>p</i> [§]		0.0114			<0.0001	
Foreign body sensation						
No.	140	141		138	142	
Mean (SD)	-0.76 (0.723)	-0.70 (0.722)		-1.09 (0.827)	-1.00 (0.775)	
Mean difference (SD)		-0.07 (0.722)	-0.19 to 0.01		-0.09 (0.801)	0.18 to 0.01
<i>p</i> [§]		0.0661			0.0311	-
Burning and stinging						
No.	140	141		138	142	
Mean (SD)	-0.57 (0.695)	-0.57 (0.706)		-0.76 (0.695)	-0.84 (0.711)	
Mean difference (SD)		0.00 (0.700)	-0.18 to 0.02		0.08 (0.703)	-0.09 to 0.04
<i>p</i> [§]		0.0985			0.4016	
Photophobia						
No.	140	141		138	142	
Mean (SD)	-0.53 (0.659)	-0.47 (0.579)		-0.72 (0.826)	-0.67 (0.726)	
Mean difference (SD)		-0.06 (0.620)	-0.14 to 0.03		-0.05 (0.777)	-0.11 to 0.02
<i>p</i> [§]		0.2093			0.2093	
Tearing						
No.	140	141		138	142	
Mean (SD)	-0.67 (0.701)	-0.53 (0.623)		-0.80 (0.751)	-0.70 (0.734)	
Mean difference (SD)		-0.14 (0.663)	-0.12 to 0.04		-0.10 (0.742)	-0.06 to 0.02
<i>p</i> [§]		0.3445			0.4156	
Discharge						
No.	140	141		138	142	
Mean (SD)	-0.53 (0.612)	-0.55 (0.614)		-0.68 (0.715)	-0.79 (0.742)	
Mean difference (SD)		0.02 (0.613)	-0.14 to 0.03		0.10 (0.729)	-0.07 to 0.04
<i>p</i> [§]		0.2182			0.6037	

CFB = change from baseline.

*Range: ocular signs (0–3), ocular symptoms (0–4). Mean (SD) baseline severities in the loteprednol etabonate suspension and olopatadine solution groups, respectively, were 1.86 (0.608) and 1.92 (0.619) for palpebral injection, 0.54 (0.670) and 0.59 (0.638) for chemosis, 0.34 (0.577) and 0.39 (0.577) for erythema, 1.61 (0.755) and 1.60 (0.735) for discomfort, 1.15 (0.843) and 1.22 (0.759) for foreign body sensation, 0.81 (0.711) and 0.94 (0.721) for burning and stinging, 0.78 (0.854) and 0.81 (0.797) for photophobia, 0.83 (0.742) and 0.74 (0.739) for tearing, and 0.74 (0.736) and 0.85 (0.746) for discharge. Missing visit 3 (day 15) observations were imputed for patients that were placed on rescue therapy or discontinued due to treatment failure, using the last observation before discontinuation of study treatment.

[†]Trademark: Alrex® (Bausch + Lomb, Rochester, New York).

[‡]Trademark: Patanol® (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

[§]Based on the ANCOVA model including treatment and center as fixed factors and baseline score as a covariate. Treatment-by-center and treatment-by-baseline interactions were tested, found to be not significant, and excluded from the final model. 95% CIs and *P* values were calculated using least squares mean.

Table IV. Treatment-emergent ocular adverse events (safety population).

	Loteprednol Etabonate Suspension* Group (n = 151)	Olopatadine Solution† Group (n = 149)	P
Patients with ≥ 1 TEAE, no. (%)	3 (2.0)	2 (1.3)	>0.9999
Specific AEs, no. (%)			
Swollen eyelid	1 (0.7)	0	>0.9999
Epidemic hemorrhagic conjunctivitis	0	1 (0.7)	0.4967
Vision blurred	0	1 (0.7)	0.4967
Instillation-site abnormal sensation	1 (0.7)	0	>0.9999
Instillation-site stinging	1 (0.7)	0	>0.9999

AE = adverse event; TEAE = treatment-emergent adverse event.

*Trademark: Alrex® (Bausch + Lomb, Rochester, New York).

†Trademark: Patanol® (S.A. Alcon-Couvreur N.V., Puurs, Belgium).

trolled studies.^{20,21} Both Dell et al²¹ and Shulman et al²⁰ compared the efficacy and tolerability of LE suspension 0.2% with those of vehicle, both were instilled bilaterally 4 times daily for 42 days in patients with moderate-to-severe signs and symptoms of SAC. In both studies, LE suspension was significantly better

than vehicle in reducing both ocular itching (-3.4 vs -2.8 units in the first study and 3.0 vs 2.6 units in the second study; $P \leq 0.008$) and bulbar conjunctival injection (-1.3 vs -0.8 units in the first study, and 1.4 vs 0.9 units in the second study; $P < 0.001$ for both) in the first 2 weeks. The proportion of patients in the LE suspension and vehicle groups, respectively, with complete resolution of ocular itching at day 14 was 54% versus 38% in the first study and 58% versus 38% in the second study, and the proportion of patients with complete resolution of bulbar conjunctival injection at day 14 was 31% versus 9% in the first study, and 36% versus 15% in the second study. No patients experienced elevated IOP of ≥ 10 mm Hg in the first study and 1 patient in each group had an IOP elevation of ≥ 10 mm Hg in the second study. An additional prospective randomized study reported that LE suspension 0.5% was more effective than vehicle in the prophylactic treatment of patients with a history of SAC.³³

To our knowledge, only one other study compared the efficacy and tolerability of LE suspension 0.2% with those of olopatadine hydrochloride 0.1% in an environmental setting. Koo et al reported that LE suspension 0.2% was more efficacious than olopatadine solution 0.1% in a randomized, double-masked, cross-over study comparing these treatments administered twice daily in 60 patients with SAC.³⁴ Although both drugs were reported to be effective in the treatment of SAC, only LE signifi-

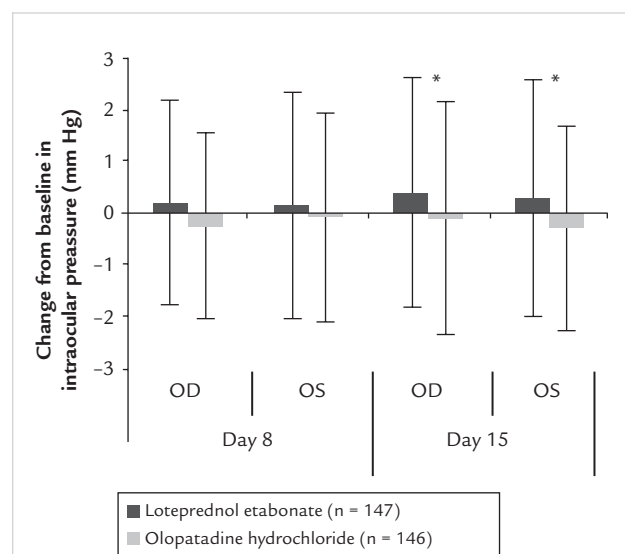


Figure 5. Mean (SD) intraocular pressure change from baseline at day 8 and day 15.

*Mean difference 0.50 mm Hg (OD) and 0.59 mm Hg (OS); $P < 0.05$. OD = right eye; OS = left eye.

cantly reduced the 12-item Ocular Surface Disease Index compared with baseline in both arms of the cross-over study ($P < 0.05$). There were no significant changes in IOP in either treatment group. In contrast, Berdy et al compared the efficacy and tolerability of LE suspension 0.2% and olopatadine hydrochloride 0.1% in a conjunctival allergen challenge study in 50 patients with allergic conjunctivitis and found olopatadine to be more efficacious than LE in reducing itching and preventing redness in the immediate early phase of the allergic response ($P < 0.05$).³⁵ The effectiveness of the treatments was not assessed more than 30 minutes after the allergen challenge, and it is unclear how much the conjunctival allergen challenge model is representative of environmental allergy.

A limitation of this study was its single-masked design. Due to physical differences in the commercial containers for LE suspension 0.2% and olopatadine solution 0.1%, the replacement of commercial labels with investigational labels was not sufficient to fully mask the patients to study treatment. However, investigators were fully masked. To mask the investigators, commercial bottles of LE suspension 0.2% and olopatadine solution 0.1% were packaged in identical kit boxes. In addition, to ensure investigators remained masked, investigators were not permitted to be present when the study coordinator dispensed the kit boxes to patients and retrieved them from patients at the end of the study.

CONCLUSION

Results from our study in Chinese patients with SAC suggest that LE suspension 0.2% was noninferior to olopatadine solution 0.1%, with few ocular and non-ocular AEs and no clinically significant increases in IOP in either treatment group.

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Patients were compensated for their participation in this study. The study treatments were provided for free and investigator fees were provided to sites to cover the study-related examinations.

CONFLICTS OF INTEREST

Drs. Elion-Mboussa, Roy, and Zhu are employees of Bausch + Lomb, Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

Supplemental Figure accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clinthera.2012.04.024>.

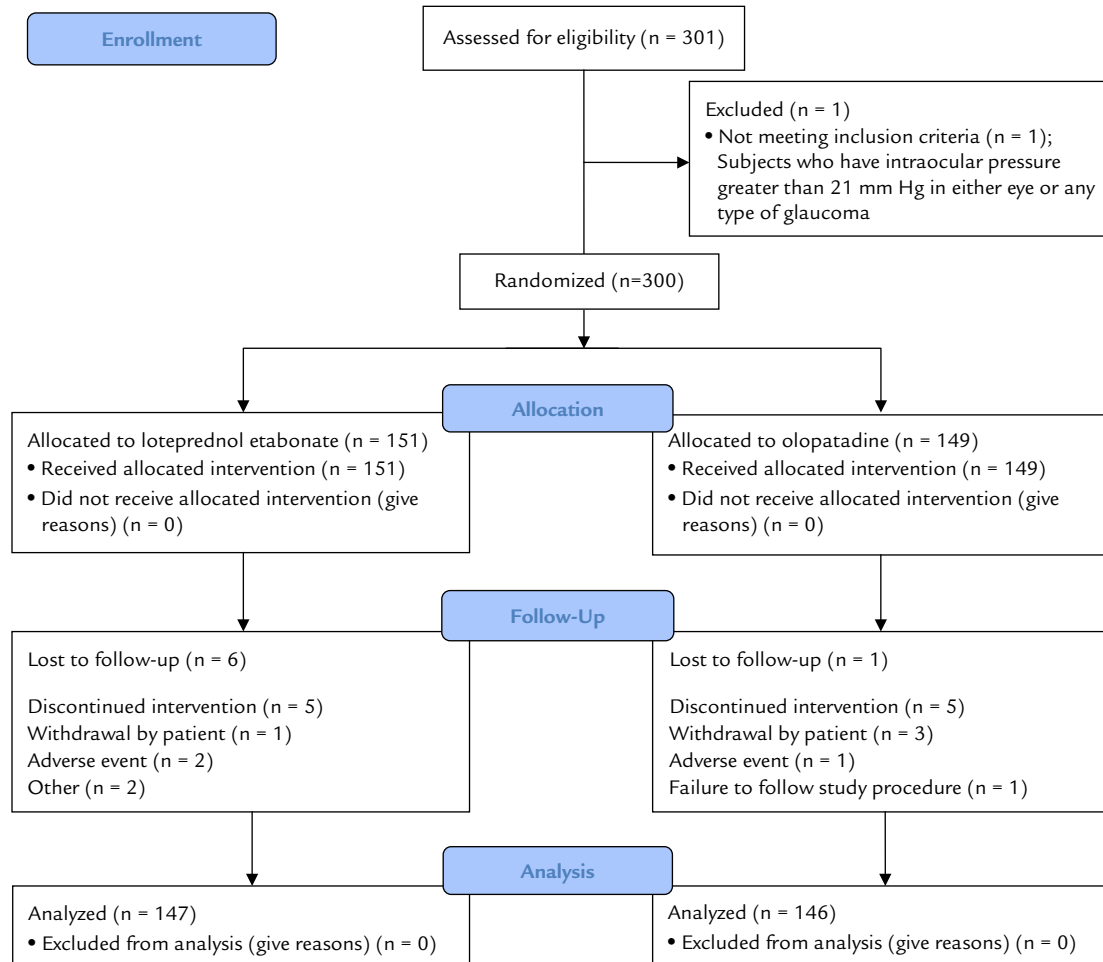
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Supplemental Figure. CONSORT (Consolidated Standards of Reporting Trials) 2010 flow diagram. Safety and efficacy of loteprednol etabonate suspension 0.2% (Alrex[®] [Bausch + Lomb, Inc., Rochester, New York]) compared with olopatadine solution 0.1% (Patanol[®] [S.A. Alcon-Couvreur N.V., Purrs, Belgium]) in the treatment of seasonal allergic conjunctivitis in Chinese patients.