



Alcaftadine 0.25% versus Olopatadine 0.1% in Preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized Study

Hiroshi Nakatani, Paul Gomes, Ron Bradford, Qiang Guo, Eleonora Safyan & David A. Hollander

To cite this article: Hiroshi Nakatani, Paul Gomes, Ron Bradford, Qiang Guo, Eleonora Safyan & David A. Hollander (2018): Alcaftadine 0.25% versus Olopatadine 0.1% in Preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized Study, Ocular Immunology and Inflammation, DOI: [10.1080/09273948.2018.1432764](https://doi.org/10.1080/09273948.2018.1432764)

To link to this article: <https://doi.org/10.1080/09273948.2018.1432764>



Published by Taylor & Francis.



Published online: 15 Mar 2018.



Submit your article to this journal [↗](#)



Article views: 5



View related articles [↗](#)



View Crossmark data [↗](#)

ORIGINAL ARTICLE

Alcaftadine 0.25% versus Olopatadine 0.1% in Preventing Cedar Pollen Allergic Conjunctivitis in Japan: A Randomized Study

Hiroshi Nakatani MD, PhD¹, Paul Gomes MS², Ron Bradford RPh³, Qiang Guo PhD⁴, Eleonora Safyan BS³, and David A. Hollander MD, MBA⁵

¹Department of Ophthalmology, Kitasato University Kitasato Institute Hospital, Tokyo, Japan, ²Allergy Research, Ora, Inc, Andover, Massachusetts, USA, ³Clinical Development, Allergan plc, Irvine, California, USA, ⁴Biostatistics, Allergan plc, Irvine, California, USA, and ⁵Global Drug Development, Allergan plc, Irvine, California, USA

ABSTRACT

Purpose: To compare alcaftadine and olopatadine ophthalmic solutions, and vehicle for preventing allergen-mediated conjunctivitis in Japanese subjects.

Methods: Japanese cedar pollen-sensitive subjects were randomized to alcaftadine 0.25%, olopatadine 0.1%, or vehicle. Ocular itching was assessed at 3, 5 (primary outcome), 7, and 15 min post-conjunctival allergen challenge (CAC) and conjunctival hyperemia assessed at 7, 15 (secondary outcome), and 20 min post-CAC. Adverse events were monitored.

Results: Overall, 240 subjects were randomized. Alcaftadine 0.25% (challenged 8 h post-dose) was significantly more effective than vehicle for prevention of itching and conjunctival hyperemia ($p < 0.001$) and noninferior to olopatadine 0.1% (challenged 4 h post-dose). Significantly lower hyperemia scores were observed in alcaftadine-treated than olopatadine-treated eyes at 7 and 15 min post-CAC ($p \leq 0.027$). Alcaftadine and olopatadine were well tolerated; no serious adverse events were reported.

Conclusion: Alcaftadine 0.25% is effective in preventing signs and symptoms of Japanese cedar pollen-induced allergic conjunctivitis.

Keywords: Alcaftadine, allergic conjunctivitis, conjunctival allergen challenge model, olopatadine

Allergic conjunctivitis is one of the most common ocular conditions affecting adult and pediatric patients.¹ An estimated 6–30% of the general population is affected by allergic conjunctivitis alone or in association with allergic rhinitis.² Studies in developed countries have reported that 14–40% of the population suffer from allergic conjunctivitis.^{3–6} In Japan, the estimated prevalence of allergic conjunctivitis is 15–20% and is most commonly associated with Japanese cedar pollen.⁷ In susceptible individuals, ocular exposure to allergens leads to

immunoglobulin E-mediated mast cell degranulation and subsequent release of histamine and other inflammatory mediators.^{8,9} Activation of histamine receptors in the conjunctiva triggers ocular itching, the hallmark symptom of allergic conjunctivitis, and other signs and symptoms including conjunctival redness, tearing, eyelid swelling, and chemosis.¹⁰

Topical ophthalmic antihistamines remain the primary therapy option for treating allergic conjunctivitis. In the United States, alcaftadine 0.25%¹¹

Received 9 August 2017; revised 18 January 2018; accepted 22 January 2018

Correspondence: Eleonora Safyan, Allergan plc, Irvine, CA 92623-9534, USA. E-mail: Safyan_Eleonora@allergan.com

Color versions of one or more of the figures in the article can be found online at [www.tandfonline.com/oi](http://www.tandfonline.com/oi/oi).

© 2018 Hiroshi Nakatani, Paul Gomes, Ron Bradford, Qiang Guo, Eleonora Safyan, and David A. Hollander. Published with license by Taylor & Francis. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

and olopatadine 0.2%¹² are approved once-daily ophthalmic solutions, and olopatadine 0.1%¹³ is an approved twice-daily ophthalmic solution for allergic conjunctivitis. In Japan, olopatadine 0.1% ophthalmic solution is approved for the treatment of allergic conjunctivitis in a four-times-daily dose, whereas alcaftadine 0.25% ophthalmic solution has yet to be approved. Alcaftadine and olopatadine are classified as dual-action anti-allergic agents, directly inhibiting histamine receptor activation and indirectly preventing allergic responses by stabilizing mast cells.¹⁴ Antihistamines have different affinities toward histamine receptors, and thus may potentially have varying effects on mast cell stabilization and anti-inflammatory properties.^{14,15}

Here we present results of a phase 3 study conducted in Japan, in which the efficacy and safety of alcaftadine 0.25% ophthalmic solution versus vehicle and olopatadine 0.1% ophthalmic solution were evaluated for the prevention of cedar pollen-related allergic conjunctivitis using the well-established conjunctival allergen challenge (CAC) model.

MATERIALS AND METHODS

Study Design and Subjects

This single-center, randomized, double-masked, vehicle- and active-controlled trial (ClinicalTrials.gov identifier: NCT02161146) was conducted at the Kitasato University Institute Hospital, Tokyo, Japan, from June 2014 to December 2014 in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines for Good Clinical Practice, and Japanese Good Clinical Practice regulations and procedures. The protocol was approved by the Institutional Review Board, and subjects provided written informed consent before study-related procedures were initiated.

Japanese adults with a history of allergic conjunctivitis and positive skin test to Japanese cedar pollen-specific allergen at the initial screening visit (visit 1), and who satisfied other inclusion/exclusion criteria (Table 1), including sufficient itching and hyperemia reactions to CAC challenges at screening visits 2 and 3 were enrolled. The study was conducted in a 6- to 9-week period and included the three screening visits and two treatment visits (Figure 1).

Allergen Screening Visits 2 and 3

At visit 2, the allergen titration visit, escalating concentrations of Japanese cedar pollen were instilled bilaterally into the conjunctival cul-de-sac every 10 min until a positive reaction was elicited (i.e., when both itching and conjunctival hyperemia

TABLE 1. Key inclusion and exclusion criteria.

Inclusion criteria

- Adults ≥ 20 years of age with a history of allergic conjunctivitis
- Positive skin test to Japanese cedar pollen-specific allergen at initial screening visit (visit 1)
- Best-corrected visual acuity ≥ 0.2 in each eye using the Landolt ring chart at visit 1
- Positive bilateral CAC reaction (ocular itching score ≥ 2.0 and ocular hyperemia score ≥ 2 in the conjunctival vessel bed) within 10 min of instillation of the last titration dose of allergen at visit 2
- Positive bilateral CAC reaction of ocular itching score ≥ 2.0 at the 5-min time point and for at least one of the 3- or 7-min time points, and ocular hyperemia score ≥ 2 in the conjunctival vessel bed for at least two of the three time points at visit 3
- Willing to discontinue wearing contact lenses during the study period, starting at least 5 days prior to visit 2

Exclusion criteria

- History of allergy or sensitivity to the study medications or prior participation with alcaftadine
- Status asthmaticus, persistent moderate or severe asthma, or moderate to severe allergic asthmatic reactions to study allergen
- History of vernal keratoconjunctivitis and/or atopic keratoconjunctivitis, or history of retinal detachment, diabetic retinopathy, or progressive retinal disease
- Presence of an active ocular infection, preauricular lymphadenopathy, or history of herpetic ocular disease any time prior to visit 4
- Systemic or ocular condition (e.g., narrow-angle glaucoma requiring medication or laser treatment, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium, or a diagnosis of dry eye) that in the opinion of the investigator could affect safety or trial results
- Ocular surgery or refractive surgery within 6 months prior to visit 1, or planned to have ocular or systemic surgery during the trial or within 30 days of completion
- Use of disallowed medications (e.g., aspirin/aspirin-containing products, H1-antagonist antihistamines and all other anti-allergy therapies, corticosteroid or mast cell stabilizers, any topical ophthalmic other than study medications) during the appropriate pre-study washout period or anticipated use during the study, or use of depot corticosteroids within 6 months before visit 2 or anticipated use during the study
- Signs and symptoms of clinically active allergic conjunctivitis (any itching or conjunctival hyperemia score >1) in either eye at the start of visit 2, 3, or 4

CAC, conjunctival allergen challenge.

scores reached ≥ 2.0 bilaterally). Post allergen challenge, itching severity was graded by subjects (on a 5-point scale; 0–4),^{16,17} as was eyelid swelling (scored on a 4-point scale; 0–3) and tearing (absent or present). Post allergen challenge, conjunctival, ciliary, and episcleral hyperemia was scored by the investigator on a 5-point ocular redness scale (0–4)^{16,17}; chemosis (scored on a 5-point scale: 0–4) and ocular mucous discharge (absent or present) were all assessed by slit-lamp biomicroscopy.

At visit 3, the allergen concentration confirmation visit, bilateral allergen challenge using the final concentration from the second visit was performed. Subjects rated ocular itching at 3, 5, 7, and 15 min and scored eyelid swelling and tearing at 7, 15, and

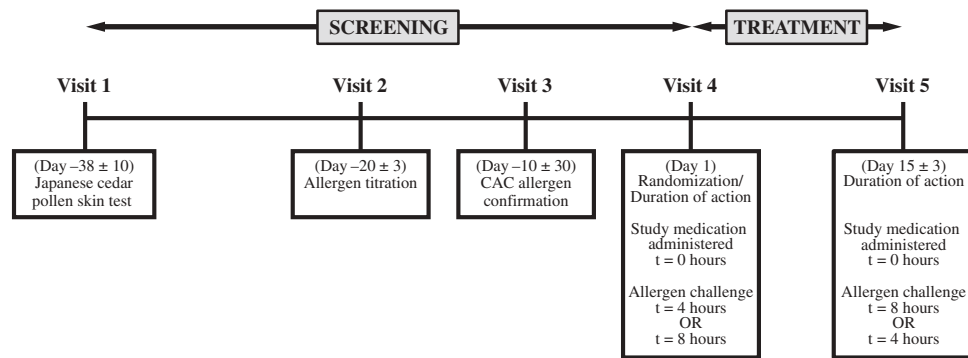


FIGURE 1. Study schema. The study included three screening visits and two treatment visits. At visit 4, subjects with confirmed positive conjunctival allergen challenge (CAC) to Japanese cedar pollen were randomized to receive study medication, and to 4-h CAC at visit 4 followed by 8-h CAC at visit 5 or 8-h CAC at visit 4 followed by 4-h CAC at visit 5.

20 min following allergen challenge. Conjunctival, ciliary, and episcleral hyperemia, chemosis, and ocular mucous discharge were scored by the investigator at 7, 15, and 20 min following the allergen challenge. Subjects who met the qualifying criteria of a post-challenge bilateral itching score ≥ 2 at 5 min and at least one of the 3- or 7-min time points, and conjunctival hyperemia score ≥ 2 at two of the three time points (7, 15, and 20 min) continued to the treatment visits.

Randomization and Treatment Visits

At visit 4, subjects were randomized 1:1:1:1 to receive one drop of either alcaftadine 0.25% ophthalmic solution bilaterally, olopatadine 0.1% ophthalmic solution (Patanol®, Alcon Laboratories, Inc., Fort Worth, TX, USA) bilaterally, vehicle (alcaftadine ophthalmic solution vehicle) bilaterally, alcaftadine 0.25%/olopatadine 0.1% contralaterally, or alcaftadine 0.25%/vehicle treatment contralaterally. In each treatment group, subjects were further randomized 1:1 based on the order of CAC assessment: 4-h CAC at visit 4 and 8-h CAC at visit 5, or 8-h CAC at visit 4 and 4-h CAC at visit 5 (Figure 1). Randomization was stratified by ocular itching score (based on the eye with the higher score) 5 min post allergen challenge at visit 3 into two strata: ocular itching score ≥ 2.0 and < 3.0 or ocular itching score ≥ 3.0 .

Randomization and treatment assignment were managed via an automated interactive voice response system/interactive web response system, based on a randomization scheme prepared by Allergan Biostatistics. Study medication was individually packaged for each eye in identical opaque 5-mL bottles. Subjects who presented at visit 5 with signs or symptoms of clinically active allergic conjunctivitis (any itching or conjunctival hyperemia score > 1) in either eye were rescheduled within 7 days and were withdrawn if signs or symptoms persisted at the

rescheduled visit. Safety was evaluated in all subjects throughout the study.

Efficacy and Safety Measures

The primary efficacy measure was ocular itching score quantified by the subject at 5 min post CAC in each eye. The secondary efficacy measure was conjunctival hyperemia assessed by the investigator at 15 min post CAC in each eye. Other efficacy measures included ocular itching scores at 3, 7, and 15 min post CAC; conjunctival hyperemia at 7 and 20 min post CAC; ciliary and episcleral hyperemia and chemosis (on biomicroscopy); and ocular mucous discharge assessed by the investigator, and eyelid swelling and tearing evaluated by the subject. Safety was assessed by monitoring adverse events, coded to system organ class and preferred terms using the Medical Dictionary for Regulatory Activities version 17.1. Other safety measures included biomicroscopy, funduscopy, and visual acuity.

Statistical Analysis

Efficacy analyses were performed using the intent-to-treat population, and data from visits 4 and 5 were pooled by treatment received in each eye. Two coprimary efficacy analyses were evaluated: (1) superiority of alcaftadine 0.25% over vehicle in ocular itching at 5 min post CAC, challenged 8 h post-dose; and (2) noninferiority of alcaftadine 0.25% in ocular itching at 5 min post CAC challenged 8 h post-dose, to olopatadine 0.1% challenged 4 h post-dose. The Wilcoxon rank-sum test treating each eye as the analysis unit was used for both primary efficacy analyses of ordinal ocular itching score data. Superiority of alcaftadine 0.25% to vehicle was demonstrated if treatment with alcaftadine 0.25% resulted in significantly lower ocular itching score compared with vehicle ($p \leq 0.05$). For noninferiority, a two-sided 95% confidence interval (CI) for the treatment difference (alcaftadine minus olopatadine)

was constructed using the Hodges–Lehmann method. Treatment with alcaftadine 0.25% was considered noninferior to olopatadine 0.1% if the upper limit of the 95% CI did not exceed 0.5 units. If alcaftadine 0.25% was noninferior to olopatadine 0.1% and achieved lower ocular itching score than olopatadine 0.1%, a test of superiority comparing alcaftadine 0.25% with challenge 8 h post-dose to olopatadine 0.1% with challenge 4 h post-dose was conducted using the Wilcoxon rank-sum test. Alcaftadine 0.25% was considered superior to olopatadine 0.1% if the resulting *p* value was ≤ 0.05 .¹⁸ As both the superiority compared to vehicle and the noninferiority compared to 0.1% olopatadine must be demonstrated for the study to be considered positive, no adjustment for multiplicity was needed to control overall type I error.

For the secondary efficacy measure, conjunctival hyperemia at 15 min, the superiority of alcaftadine 0.25% over vehicle, and noninferiority of alcaftadine 0.25% to olopatadine 0.1%, were analyzed as described for the primary efficacy analysis. For other efficacy analyses, continuous variables were summarized by descriptive statistics and categorical variables were summarized by frequency and percentage. Two-sided *p* values ≤ 0.05 were considered statistically significant. For safety, assessed on all randomized subjects who received at least one dose of study treatment, incidence rates of treatment-emergent adverse events (TEAEs) regardless of causality, treatment-related TEAEs, and serious adverse events were summarized for each treatment group.

Sample size was determined based on the test of noninferiority of alcaftadine 0.25% to olopatadine 0.1%, which required the larger sample size, and assumed a common standard deviation of 1.15 units per treated eye group. To assign subjects into one of five arms (1:1:1:1:1 randomization), the allocation ratio

of eyes to each treatment (alcaftadine 0.25%, olopatadine 0.1%, or vehicle) was 4:3:3. Assuming an expected treatment difference of 0.05 units between alcaftadine 0.25% and olopatadine 0.1% (alcaftadine minus olopatadine) with a one-sided α of 0.025, to achieve 90% power for a noninferiority margin of 0.5 units, 168 eyes in the alcaftadine group and 126 eyes in the olopatadine group were required. With a 4:3 (alcaftadine to vehicle) allocation ratio, a sample size of 168 eyes in the alcaftadine group and 126 eyes in the vehicle group was determined to provide greater than 90% power to detect a superiority difference of one unit between the two treatment groups, with a two-sided α of 0.05. Allowing for a discontinuation rate of approximately 12%, a total of 240 subjects were to be enrolled (42 subjects assigned into each of the five treatment arms). Sample size and power calculations were performed using PASS 2008 software (NCSS, LLC, Kaysville, UT, USA), based on Wilcoxon–Mann–Whitney test of the difference between two means.^{19,20}

RESULTS

Subject Disposition and Baseline Characteristics

A total of 240 subjects, comprising the intent-to-treat population, were randomized (Figure 2). Subject demographics and characteristics were similar between groups (Table 2). Based on ocular itching score of the worse eye at visit 3, 129 (53.8%) subjects were categorized in the first stratum (ocular itch score ≥ 2 and < 3) and 111 (46.3%) were categorized in the second stratum (ocular itch score ≥ 3). In

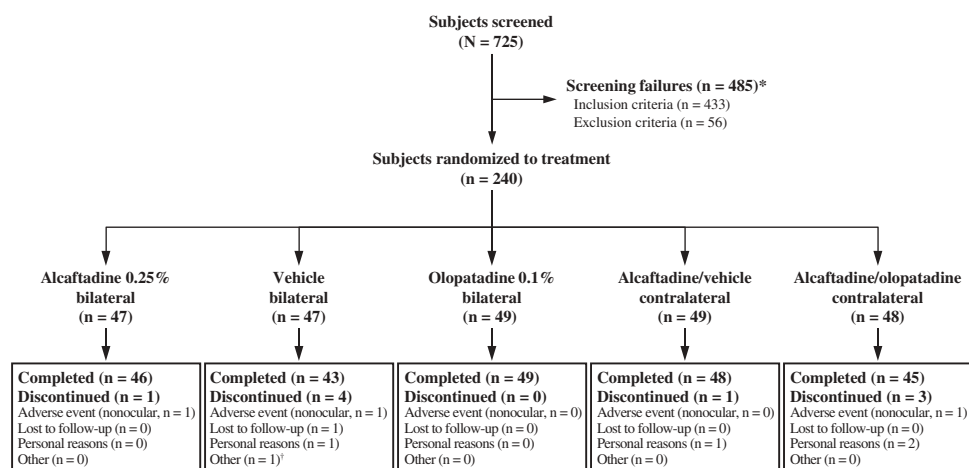


FIGURE 2. Subject flow chart. Subjects were randomized 1:1:1:1:1 to receive bilateral or contralateral treatment with alcaftadine 0.25%, olopatadine 0.1%, or vehicle. Subjects assigned vehicle treatment received the alcaftadine ophthalmic solution vehicle. *Four subjects failed both inclusion and exclusion criteria. [†]Timing of interactive voice response system kit assignment.

TABLE 2. Subject demographics at screening visit 1 and itching stratum assessed at screening visit 3 (intent-to-treat population).

Characteristic	Treatment group					All subjects (N = 240)
	Alcaftadine/ alcaftadine (n = 47)	Vehicle/ vehicle (n = 47)	Olopatadine/ olopatadine (n = 49)	Alcaftadine/ vehicle (n = 49)	Alcaftadine/ olopatadine (n = 48)	
Age, mean (SD), years	33.2 (10.0)	36.9 (10.4)	38.7 (11.3)	35.4 (11.1)	35.6 (11.2)	36 (10.9)
Sex, n (%)						
Male	30 (63.8)	25 (53.2)	25 (51.0)	23 (46.9)	29 (60.4)	132 (55.0)
Female	17 (36.2)	22 (46.8)	24 (49.0)	26 (53.1)	19 (39.6)	108 (45.0)
Itching stratum, ^a n (%)						
≥2 and <3	26 (55.3)	26 (55.3)	25 (51.0)	27 (55.1)	25 (52.1)	129 (53.8)
≥3	21 (44.7)	21 (44.7)	24 (49.0)	22 (44.9)	23 (47.9)	111 (46.3)

SD, standard deviation.

^aStratified by ocular itching score on worse eye 5 min post conjunctival allergen challenge with cedar pollen at visit 3.

all, 96.3% (231/240) completed the study; subjects discontinued due to personal reasons (4), adverse events (3), lost to follow-up (1), and timing of interactive voice response system kit assignment (1).

Efficacy Outcomes

Efficacy analyses were performed by treatment group: alcaftadine 0.25%-treated eyes ($n = 191$), olopatadine 0.1%-treated eyes ($n = 146$), and vehicle-treated eyes ($n = 143$). Ocular itching scores at screening visits 2 and 3 were similar among treatment groups. Ocular itching score in alcaftadine-treated eyes (median = 0.00) at 5 min post CAC, challenged 8 h post-dose (primary efficacy variable) was statistically significantly lower than ocular itching score in vehicle-treated eyes (median = 1.50) from Wilcoxon rank-sum test, demonstrating superiority of alcaftadine over vehicle ($p < 0.001$; Table 3). Alcaftadine 0.25%-treated eyes also demonstrated statistically superior itching scores versus vehicle-treated eyes at all other post CAC time points (3, 7, and 15 min) ($p < 0.001$; Table 3). At 4 h post-dose, ocular itching scores were also statistically significantly lower in alcaftadine-treated eyes than in vehicle-treated eyes ($p < 0.001$) at all post CAC time points (3, 5, 7, and 15 min). At 5 min post CAC, ocular itching scores in alcaftadine 0.25%-treated eyes (median = 0.00) challenged 8 h post-dose were comparable to olopatadine 0.1%-treated eyes (median = 0.00) challenged 4 h post-dose (Table 3). The upper limit of the 95% CI for the treatment difference (95% CI: 0.00, 0.00) was below 0.5, demonstrating that alcaftadine 0.25% 8 h post-dose was noninferior to olopatadine 0.1% 4 h post-dose. Ocular itching in alcaftadine 0.25%-treated eyes was noninferior to olopatadine 0.1%-treated eyes at all other time points assessed post CAC (Table 3). Figure 3 presents mean ocular itching scores at baseline and 5 min post CAC for each treatment group.

Conjunctival hyperemia score at 15 min post CAC (secondary efficacy variable) was statistically significantly lower in alcaftadine 0.25%-treated eyes (median = 1.00)

challenged 8 h post-dose compared with vehicle-treated eyes (median = 1.50) from Wilcoxon rank-sum test ($p < 0.001$; Table 3). Alcaftadine was superior to vehicle treatment at all other time points (7 and 20 min) ($p < 0.001$; Table 3). Additionally, alcaftadine 0.25% when challenged at 4 h post-dose demonstrated statistical superiority over vehicle at all post CAC time points (7, 15, and 20 min, $p < 0.001$). At 15 min post CAC, the conjunctival hyperemia score in alcaftadine 0.25%-treated eyes (median = 1.00) challenged 8 h post-dose was noninferior to olopatadine 0.1%-treated eyes (median = 1.50) challenged 4 h post-dose (Table 3); the upper limit of the 95% CI for treatment difference (95% CI: -0.50, 0.00) was below 0.5. Alcaftadine 0.25% was noninferior to olopatadine 0.1% at the other post CAC time points (7 and 20 min) with upper limits of the 95% CI below 0.5 (Table 3). In addition, alcaftadine 0.25%-treated eyes when challenged 8 h post-dose had statistically significantly lower conjunctival hyperemia scores compared with olopatadine 0.1%-treated eyes challenged 4 h post-dose, at 7 and 15 min post CAC ($p < 0.05$; Table 3). Conjunctival hyperemia was numerically lower in alcaftadine 0.25%-treated eyes compared with olopatadine 0.1%-treated eyes at 20 min post CAC, but did not reach statistical significance. A sensitivity analysis assessing the effect of the correlation between two eyes and period effect demonstrated statistically significant differences in conjunctival hyperemia scores between alcaftadine 0.25%-treated eyes challenged 8 h post-dose compared with olopatadine 0.1%-treated eyes challenged 4 h post-dose, at all time points (7, 15, and 20 min) (Table 3). Mean conjunctival hyperemia scores at baseline and 15 min post CAC for each treatment group are presented in Figure 4.

Alcaftadine 0.25% treatment with allergen challenge 4 or 8 h post-dose demonstrated numerically lower ciliary and episcleral hyperemia scores, and chemosis scores compared with vehicle. Alcaftadine 0.25%-treated eyes challenged 8 h post-dose achieved statistically significantly lower ciliary hyperemia scores ($p \leq 0.037$) at 7 and 15 min post CAC, and episcleral hyperemia ($p = 0.011$) and chemosis ($p = 0.006$) scores at 7 min

TABLE 3. Treatment differences in ocular itch (primary variable) and conjunctival hyperemia (secondary variable) scores post CAC, after treatment instillation during study visits 4 and 5 (intent-to-treat population)^a.

Time point post CAC	Alcaftadine 0.25% (<i>n</i> = 186)	Olopatadine 0.1% (<i>n</i> = 145)	Vehicle (<i>n</i> = 136)	Treatment difference (95% CI)	
				Alcaftadine vs. vehicle	Alcaftadine vs. olopatadine
Ocular itching, min, median ^b					
3	0.00	0.00	1.00	−0.50 (−1.00, −0.50) <i>p</i> < 0.001	0.00 (0.00, 0.00) <i>p</i> = 0.725
5	0.00	0.00	1.50	−1.00 (−1.00, −1.00) <i>p</i> < 0.001	0.00 (0.00, 0.00) <i>p</i> = 0.860
7	0.00	0.50	1.50	−1.00 (−1.50, −1.00) <i>p</i> < 0.001	0.00 (0.00, 0.00) <i>p</i> = 0.817
15	0.50	0.50	1.00	−1.00 (−1.00, −0.50) <i>p</i> < 0.001	0.00 (0.00, 0.00) <i>p</i> = 0.976
Ocular itching sensitivity analysis, min, mean (SD) ^c					
3	0.20 (0.42)	0.17 (0.32)	1.04 (0.85)	−0.73 (−0.86, −0.60) <i>p</i> < 0.001	0.04 (−0.04, 0.12) <i>p</i> = 0.302
5	0.33 (0.52)	0.29 (0.41)	1.48 (0.90)	−1.02 (−1.17, −0.87) <i>p</i> < 0.001	0.04 (−0.07, 0.14) <i>p</i> = 0.487
7	0.41 (0.59)	0.38 (0.49)	1.67 (0.96)	−1.08 (−1.24, −0.93) <i>p</i> < 0.001	0.01 (−0.11, 0.13) <i>p</i> = 0.850
15	0.50 (0.64)	0.48 (0.55)	1.53 (1.04)	−0.91 (−1.07, −0.75) <i>p</i> < 0.001	0.01 (−0.11, 0.13) <i>p</i> = 0.865
Conjunctival hyperemia, min, median ^b					
7	0.50	1.00	1.00	−0.50 (−0.50, −0.50) <i>p</i> < 0.001	0.00 (−0.50, 0.00) <i>p</i> = 0.015
15	1.00	1.50	1.50	−0.50 (−0.50, −0.50) <i>p</i> < 0.001	0.00 (−0.50, 0.00) <i>p</i> = 0.027
20	1.00	2.00	2.00	−0.50 (−0.50, 0.00) <i>p</i> < 0.001	0.00 (−0.50, 0.00) <i>p</i> = 0.080
Conjunctival hyperemia sensitivity analysis, min, mean (SD) ^c					
7	0.67 (0.58)	0.89 (0.75)	1.14 (0.76)	−0.39 (−0.50, −0.28) <i>p</i> < 0.001	−0.30 (−0.42, −0.17) <i>p</i> < 0.001
15	1.15 (0.77)	1.34 (0.85)	1.61 (0.82)	−0.26 (−0.37, −0.15) <i>p</i> < 0.001	−0.27 (−0.42, −0.12) <i>p</i> < 0.001
20	1.40 (0.88)	1.52 (0.88)	1.76 (0.86)	−0.13 (−0.24, −0.02) <i>p</i> = 0.025	−0.20 (−0.36, −0.04) <i>p</i> = 0.013

CAC, conjunctival allergen challenge; CI, confidence interval; SD, standard deviation.

^aAllergen challenge with cedar pollen 8 h after alcaftadine 0.25% and vehicle treatment, and 4 h after olopatadine 0.1% treatment.

^b*p* Values calculated based on Wilcoxon rank-sum test by treating each eye as the analysis unit; the Hodges–Lehmann method was used for the point estimate and the 95% CI of the difference (location shift).

^cSensitivity analysis investigating effect of the correlation between two eyes and period effect, using a mixed-effect model with treatment and visit as fixed effects and subject as a random effect.

post CAC compared with vehicle-treated eyes (Table 4). Eyelid swelling scores were statistically significantly lower following treatment with alcaftadine 0.25% when challenged 8 h post-dose at all time points assessed (7, 15, and 20 min) compared with vehicle (*p* < 0.001; Table 4). Additionally, statistically significantly greater proportions of eyes treated with alcaftadine 0.25% challenged 4 or 8 h post-dose had no tearing compared with vehicle-treated eyes at 7, 15, and 20 min post CAC (*p* < 0.001) (Table 4). The incidence of ocular mucous discharge was lower in alcaftadine 0.25%-treated eyes when challenged 8 h post-dose compared with vehicle-treated eyes, but differences did not reach statistical significance (Table 4).

No significant differences were observed between alcaftadine 0.25%-treated eyes challenged 8 h post-dose and olopatadine 0.1%-treated eyes challenged 4 h post-dose in mean ciliary hyperemia, episcleral

hyperemia, chemosis, and eyelid swelling scores at all time points (7, 15, and 20 min) assessed (Table 4). Additionally, no differences were observed between alcaftadine 0.25% and olopatadine 0.1% in the proportion of eyes without tearing and ocular mucous discharge at all the post CAC time points (Table 4).

Safety

Overall, TEAEs occurred in 22.4% of subjects in the alcaftadine/vehicle group, 21.3% in the vehicle/vehicle group, 14.9% in the alcaftadine/alcaftadine group, 14.6% in the alcaftadine/olopatadine group, and 12.2% in the olopatadine/olopatadine group. The majority of TEAEs were nonocular, and the

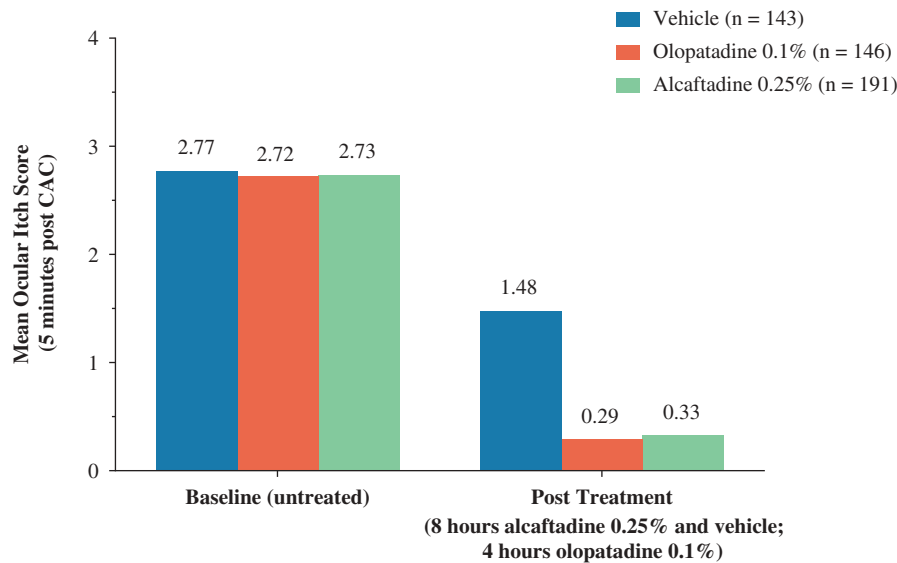


FIGURE 3. Ocular itching following treatment with alcaftadine 0.25%. Mean itching scores at baseline and when challenged with cedar pollen 8 h after alcaftadine 0.25% and vehicle treatment, and 4 h after olopatadine 0.1% treatment, at 5 min post conjunctival allergen challenge (CAC; primary variable, intent-to-treat population).

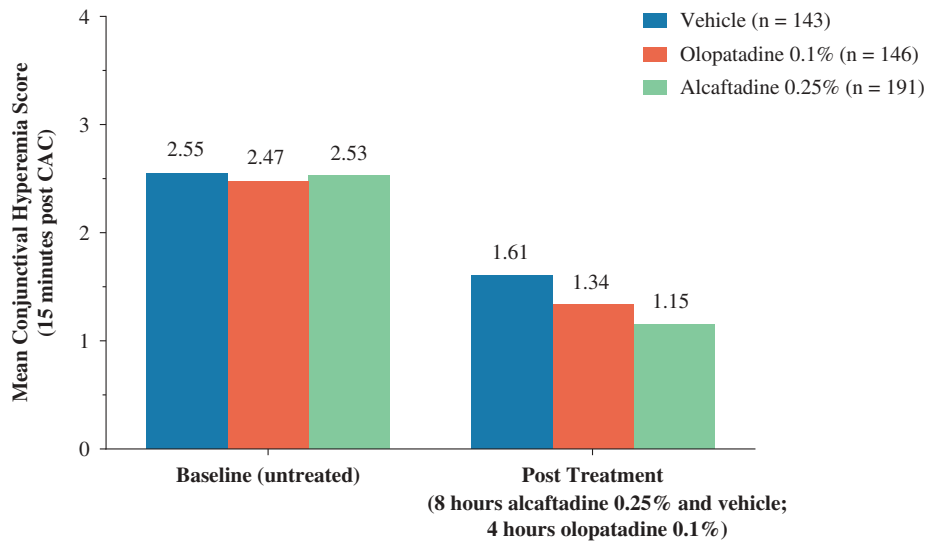


FIGURE 4. Conjunctival hyperemia following treatment with alcaftadine 0.25%. Conjunctival hyperemia scores at baseline and when challenged with cedar pollen 8 h after alcaftadine 0.25% and vehicle treatment, and 4 h after olopatadine 0.1% treatment, at 15 min post conjunctival allergen challenge (CAC; secondary variable, intent-to-treat population).

most commonly reported (occurring in $\geq 5\%$ of subjects in any treatment group) were oropharyngeal discomfort (12.8% vehicle/vehicle group, 6.1% olopatadine/olopatadine group), oropharyngeal pain (6.4% vehicle/vehicle group), rhinorrhea (6.4% vehicle/vehicle group), and nasopharyngitis (6.4% alcaftadine/alcaftadine group). Ocular TEAEs were infrequent, occurring in 1.6% (3/191) of alcaftadine-treated eyes (chalazion, conjunctival follicles, retinal hemorrhage) and 2.1% (3/143) of vehicle-treated eyes (chalazion, conjunctival follicles, eye pruritus); no ocular adverse events were reported in

olopatadine-treated eyes. Three TEAEs, all mild in severity, were considered by the investigator to be treatment-related, somnolence (alcaftadine/alcaftadine group), thirst (alcaftadine/olopatadine group), and eye pruritus (vehicle/vehicle group).

No deaths or other serious adverse events were reported. The three discontinuations due to adverse events, one subject with oropharyngeal discomfort and rhinorrhea (alcaftadine/alcaftadine group), one subject with oropharyngeal discomfort and wheezing (vehicle/vehicle group), and one subject with chalazion (alcaftadine/olopatadine group), were

TABLE 4. Summary of other efficacy variables post CAC after treatment instillation (intent-to-treat population)^a

Time point post CAC	Alcaftadine 0.25% (<i>n</i> = 186)	Olopatadine 0.1% (<i>n</i> = 145)	Vehicle (<i>n</i> = 136)	<i>p</i> Value ^b	
				Alcaftadine vs. vehicle	Alcaftadine vs. olopatadine
Ciliary hyperemia score, min, mean (SD)					
7	0.28 (0.47)	0.34 (0.51)	0.48 (0.64)	0.006	0.211
15	0.48 (0.66)	0.59 (0.69)	0.69 (0.81)	0.037	0.123
20	0.60 (0.82)	0.69 (0.73)	0.74 (0.87)	0.155	0.112
Episcleral hyperemia score, min, mean (SD)					
7	0.27 (0.47)	0.24 (0.46)	0.44 (0.61)	0.011	0.461
15	0.46 (0.63)	0.47 (0.67)	0.62 (0.78)	0.154	0.877
20	0.57 (0.78)	0.54 (0.70)	0.69 (0.85)	0.291	0.901
Chemosis score, min, mean (SD)					
7	0.09 (0.28)	0.11 (0.33)	0.21 (0.42)	0.006	0.941
15	0.22 (0.46)	0.19 (0.44)	0.36 (0.66)	0.141	0.263
20	0.32 (0.58)	0.30 (0.55)	0.44 (0.77)	0.381	0.534
Eyelid swelling score, min, mean (SD)					
7	0.04 (0.19)	0.04 (0.20)	0.21 (0.48)	<0.001	0.863
15	0.15 (0.41)	0.19 (0.41)	0.47 (0.70)	<0.001	0.136
20	0.22 (0.46)	0.23 (0.47)	0.58 (0.73)	<0.001	0.661
No tearing, min, n/N (%)					
7	177/186 (95.2)	142/145 (97.9)	107/136 (78.7)	<0.001	0.181
15	170/186 (91.4)	134/145 (92.4)	98/136 (72.1)	<0.001	0.738
20	171/186 (91.9)	129/145 (89.0)	99/136 (72.8)	<0.001	0.357
No mucous discharge, min, n/N (%)					
7	182/186 (97.8)	145/145 (100)	128/136 (94.1)	0.081	0.134 ^c
15	178/186 (95.7)	143/145 (98.6)	125/136 (91.9)	0.154	0.195 ^c
20	175/186 (94.1)	138/145 (95.2)	127/136 (93.4)	0.796	0.665

CAC, conjunctival allergen challenge; SD, standard deviation.

^aAllergen challenge with cedar pollen 8 h after alcaftadine 0.25% and vehicle treatment, and 4 h after olopatadine 0.1% treatment.

^b*p* Values calculated based on Wilcoxon rank-sum test by treating each eye as the analysis unit for the median treatment difference for ciliary hyperemia, episcleral hyperemia, chemosis, and eyelid swelling; *p* values calculated using Pearson's chi-square test for between-group comparisons for tearing and ocular mucous.

^c*p* Value based on Fisher's exact test for between-group comparisons for ocular mucous at 15 and 20 min.

considered nontreatment-related by the investigator and all resolved without sequelae. No safety concerns were found on biomicroscopy, funduscopy, and visual acuity assessments.

DISCUSSION

Allergic conjunctivitis is common in Japan, most often associated with exposure to Japanese cedar pollen.⁷ This study evaluated the efficacy and safety of alcaftadine 0.25% ophthalmic solution in preventing signs and symptoms of cedar pollen-related allergic conjunctivitis in Japanese adults. The study was conducted using the CAC model, the same model which was used to establish efficacy of alcaftadine in the US and olopatadine in the US and Japan. While this model does not evaluate efficacy during chronic exposure to allergen or following rechallenge, the results are considered to be valid and representative of efficacy in real-world conditions.

Alcaftadine 0.25% was superior to vehicle in preventing both itching and conjunctival hyperemia when dosed 8 h prior to allergen challenge. Alcaftadine 0.25% dosed 8 h prior to allergen challenge was

noninferior to olopatadine 0.1% dosed 4 h prior to allergen challenge in preventing ocular itching and conjunctival hyperemia. In addition, alcaftadine 0.25% dosed 8 h prior to allergen challenge was statistically superior to olopatadine 0.1% dosed 4 h prior to allergen challenge in preventing conjunctival hyperemia at two of three time points evaluated ($p \leq 0.027$). Treatment with alcaftadine 0.25% was well tolerated with a similar safety profile to that described in previous studies.^{21–23} No subjects discontinued because of TEAEs, and there were no deaths or serious adverse events during the conduct of the study.

The pharmacokinetics of alcaftadine 0.25% administered once daily in Japanese subjects are comparable to those in non-Japanese subjects (data on file). Using the CAC model, comparative studies of alcaftadine and olopatadine have been conducted previously in non-Japanese subjects. In two similarly designed trials, once-daily treatment with alcaftadine 0.25% was safe and effective in preventing signs and symptoms of allergic conjunctivitis at both 16 and 24 h post treatment.^{22,23} Significantly lower mean itching scores were achieved following treatment with alcaftadine 0.25% compared with

olopatadine 0.2%, particularly at the earliest time point assessed (3 min) post CAC, and over all time points (3, 5, and 7 min) combined.^{22,23} Further analyses showed that alcaftadine 0.25% was effective in preventing ocular itching triggered by both seasonal and perennial allergens, compared with placebo.²⁴

Among ocular antihistamines, alcaftadine is unique in that it exhibits antagonistic activity against H1 and H2 receptors, and has demonstrated activity against H4 receptors.^{14,25,26} Alcaftadine 0.25% has shown an earlier onset of action than olopatadine 0.1%, achieving lower itching scores 3 min post CAC at 15 min post treatment, and a sustained duration of action up to 24 h post treatment.^{21–23} Alcaftadine has also demonstrated a greater effect than olopatadine on reducing eosinophil recruitment and maintaining stability of the epithelial junctional protein, zonula occludens-1, in a murine model of allergic conjunctivitis.²⁷ There is evidence that pro-inflammatory cytokines can disrupt the corneal epithelial barrier and increase cell permeability.²⁸ Further studies are recommended to establish whether the differences observed between alcaftadine and olopatadine reflect a greater ability of alcaftadine to prevent allergen-activated disruption of conjunctival epithelial barriers.

In the current study, alcaftadine 0.25% dosed 8 h prior to allergen challenge (supporting twice-daily dosing) was found to be as effective or superior to olopatadine 0.1% dosed 4 h prior to allergen challenge (supporting four times daily dosing) in preventing signs and symptoms of allergic conjunctivitis secondary to cedar pollen. Overall, this study demonstrates the safety and efficacy for the use of alcaftadine 0.25% for the prevention of signs and symptoms associated with allergic conjunctivitis triggered by Japanese cedar pollen.

ACKNOWLEDGMENTS

The authors would like to thank the subjects who participated in this study. Writing and editorial assistance was provided to the authors by Kakuri M. Omari, PhD, of Evidence Scientific Solutions, Philadelphia, PA, USA. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

DECLARATION OF INTEREST

Paul Gomes is an employee of Ora, Inc. Ron Bradford, Qiang Guo and Eleonora Safyan are employees of Allergan plc. David A. Hollander was an employee of Allergan plc when the study was conducted. The study was sponsored by Allergan plc, Dublin, Ireland.

FUNDING

This work was supported by Allergan plc.

REFERENCES

1. Mortemousque B, Fauquert JL, Chiambaretta F, et al. [Conjunctival provocation test: recommendations]. *J Fr Ophthalmol*. 2006;29:837–846.
2. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol*. 2015;15:482–488.
3. Blaiss MS. Allergic rhinoconjunctivitis: burden of disease. *Allergy Asthma Proc*. 2007;28:393–397.
4. Leonardi A, Bogacka E, Fauquert JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy*. 2012;67:1327–1337.
5. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. *J Allergy Clin Immunol*. 2010;126:778–783.e776.
6. Björkstén B, Clayton T, Ellwood P, et al. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. 2008;19:110–124.
7. Takamura E, Uchio E, Ebihara N, et al. Japanese guideline for allergic conjunctival diseases. *Allergol Int*. 2011;60:191–203.
8. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. *Curr Opin Allergy Clin Immunol*. 2007;7:429–435.
9. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol*. 2005;115:118–122.
10. Collum L, Kilmartin DJ. Acute allergic conjunctivitis. In: Abelson MD, ed. *Allergic Diseases of the Eye*. Philadelphia: W.B. Saunders Co; 2000:108–132.
11. Lastacaft® (alcaftadine ophthalmic solution) 0.25% [prescribing information]. Irvine, CA: Allergan plc; 2015. http://www.allergan.com/assets/pdf/lastacaft_pi.pdf. Accessed November 10, 2016.
12. Pataday® (olopatadine hydrochloride ophthalmic solution) 0.2% [prescribing information]. Fort Worth, TX: Alcon a Novartis Company; 2010. http://ecatalog.alcon.com/pi/Pataday_us_en.pdf. Accessed November 10, 2016.
13. Patanol® (olopatadine hydrochloride ophthalmic solution) 0.1% [prescribing information]. Fort Worth, TX: Alcon a Novartis Company; 2007. http://ecatalog.alcon.com/pi/Patanol_us_en.pdf. Accessed November 10, 2016.
14. Wade L, Bielory L, Rudner S. Ophthalmic antihistamines and H1-H4 receptors. *Curr Opin Allergy Clin Immunol*. 2012;12:510–516.
15. Bielory L, Ghafoor S. Histamine receptors and the conjunctiva. *Curr Opin Allergy Clin Immunol*. 2005;5:437–440.
16. Abelson MB, Chambers WA, Smith LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol*. 1990;108:84–88.
17. Abelson MB. Evaluation of olopatadine, a new ophthalmic antiallergic agent with dual activity, using the conjunctival allergen challenge model. *Ann Allergy Asthma Immunol*. 1998;81:211–218.
18. Morikawa T, Yoshida M. A useful testing strategy in phase III trials: combined test of superiority and test of equivalence. *J Biopharm Stat*. 1995;5:297–306.

19. Wang H, Chen B, Chow SC. Sample size determination based on rank tests in clinical trials. *J Biopharm Stat.* [2003](#);13:735–751.
20. Julious SA. Sample sizes for clinical trials with normal data. *Stat Med.* [2004](#);23:1921–1986.
21. Greiner JV, Edwards-Swanson K, Ingerman A. Evaluation of alcaftadine 0.25% ophthalmic solution in acute allergic conjunctivitis at 15 minutes and 16 hours after instillation versus placebo and olopatadine 0.1%. *Clin Ophthalmol.* [2011](#);5:87–93.
22. Ackerman S, D'Ambrosio F Jr., Greiner JV, et al. A multicenter evaluation of the efficacy and duration of action of alcaftadine 0.25% and olopatadine 0.2% in the conjunctival allergen challenge model. *J Asthma Allergy.* [2013](#);6:43–52.
23. McLaurin EB, Marsico NP, Ackerman SL, et al. Ocular itch relief with alcaftadine 0.25% versus olopatadine 0.2% in allergic conjunctivitis: pooled analysis of two multicenter randomized clinical trials. *Adv Ther.* [2014](#);31:1059–1071.
24. Ciolino JB, McLaurin EB, Marsico NP, et al. Effect of alcaftadine 0.25% on ocular itch associated with seasonal or perennial allergic conjunctivitis: a pooled analysis of two multicenter randomized clinical trials. *Clin Ophthalmol.* [2015](#);9:765–772.
25. Gallois-Bernos A, Thurmond RL. Pharmacology of alcaftadine, a new antihistamine for ocular allergy. *Invest Ophthalmol Vis Sci.* [2011](#);52:e6426.
26. Namdar R, Valdez C. Alcaftadine: a topical antihistamine for use in allergic conjunctivitis. *Drugs Today (Barc).* [2011](#);47:883–890.
27. Ono SJ, Lane K. Comparison of effects of alcaftadine and olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. *Drug Des Devel Ther.* [2011](#);5:77–84.
28. Contreras-Ruiz L, Schulze U, García-Posadas L, et al. Structural and functional alteration of corneal epithelial barrier under inflammatory conditions. *Curr Eye Res.* [2012](#);37:971–981.