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ORIGINAL ARTICLE



Efficacy of Alcaftadine 0.25% (AGN-229666) for Once-daily Prevention of Cedar-Pollen Allergic Conjunctivitis: A Phase 3 Randomized Study

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ABSTRACT

Purpose: This study evaluated the efficacy and safety of once-daily Alcaftadine 0.25% (AGN-229666) for prevention of signs and symptoms of Japanese cedar-pollen allergic conjunctivitis.

Methods: This was a single-center, placebo-, and comparator-controlled study using the Ora-CAC[®] model of allergic conjunctivitis. The primary endpoint was ocular itching 16 hours after Alcaftadine 0.25% instillation; efficacy at 16 hours was compared with 0.1% Olopatadine, 4 hours after instillation. Secondary endpoints included conjunctival hyperemia.

Results: 263 Japanese subjects were enrolled; 224 completed the trial. Alcaftadine 0.25% was statistically superior to vehicle for relief of ocular itching at 16 hours ($p < .0001$). Alcaftadine 0.25% at 16 hours was non-inferior to Olopatadine at 4 hours. Alcaftadine 0.25% was significantly better than vehicle for relief of conjunctival hyperemia. All treatments showed a low frequency of ocular adverse events.

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

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Alcaftadine; allergic conjunctivitis; Ora-CAC[®] model; Olopatadine; cedar-Pollen; randomized

Allergic conjunctivitis (AC) is a common ocular disorder among both adult and pediatric populations.^{1,2} Recent estimates suggest as many as 1 in 3 of individuals experience some degree of seasonal or perennial AC, either alone or in association with allergic rhinitis.^{1,3,4} In Japan, the estimated prevalence of AC is 15–20% and is most commonly associated with Japanese cedar pollen.⁵ For those individuals with AC, ocular exposure to allergens initiates an IgE-mediated mast cell degranulation leading to release of histamine and other inflammatory mediators.^{6–8} Activation of histamine receptors in the conjunctiva triggers ocular itching, hyperemia, and tearing; in more severe cases eyelid swelling and chemosis may also occur.^{7,8} The initial response to histamine, itch, can also initiate a cycle of eye rubbing that exacerbates the mast cell response, leading to more histamine release and a greater symptomatic response; thus itch is both the hallmark of AC and the key to alleviating the signs and symptoms of the condition.⁹

Topical antihistamines represent the primary therapy option for treating AC.¹⁰ Alcaftadine 0.25% is approved for once-daily use in the United States¹¹ but is not approved for use in Japan. Olopatadine is approved in once-daily (0.7%, 0.2%) and twice-daily (0.1%) dosing formulations in the US and is also approved as a four-times-daily formulation (Olopatadine 0.1%) in Japan.^{12–14} Both Alcaftadine and Olopatadine are classified as dual-action anti-allergic agents as they are competitive inhibitors of histamine receptor activation and also mediate a stabilization of mast cells that inhibits IgE-mediated degranulation.¹⁵ Alcaftadine is known to protect epithelial

tight junction protein markers from allergic inflammation-based degradation while Olopatadine, in contrast, failed to prevent tight junction protein degradation.¹⁶ Differences in antihistamine efficacy in relief of AC are potentially due to differences in the relative potency in mediating histamine receptor activation and in the ability of Alcaftadine to prevent epithelial gap junction degradation.^{15,17}

Recently we reported results of a phase 3 study conducted in Japan in which the efficacy and safety of Alcaftadine 0.25% ophthalmic solution was evaluated at 8 hours after instillation for the prevention of cedar-pollen-related allergic conjunctivitis.¹⁸ This study was conducted using conjunctival allergen challenge¹⁹ model, a clinical model that employs controlled provocations of allergic response to quantify efficacy of potential anti-allergic therapeutics.^{19,20} In that study, Alcaftadine was significantly more effective than vehicle for prevention of itching and conjunctival hyperemia ($p < .001$) and non-inferior to Olopatadine 0.1% (challenged 4 h post-dose).

In the present study, we tested whether Alcaftadine efficacy could be sustained over a longer time period of 16 hours. This duration is sufficient for once-daily dosing and thus would represent a significant therapeutic asset. To do this, we again used the Ora-CAC[®] model and the positive comparator, Olopatadine 0.1%.

Materials and Methods

A prospective, single-center, double-masked, randomized, vehicle- and active-controlled, Ora Ora-CAC[®] conjunctival

allergen challenge model study was conducted at the Kitasato University Kitasato Institute Hospital, Tokyo, Japan. (the University Hospital Medical Information Network identifier: UMIN000028492) All study procedures were conducted in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice regulations and procedures. The protocol was approved by the Institutional Review Board, and all subjects were provided written informed consent before study-related procedures were initiated.

Potential subjects were Japanese adults 20 years of age or older with a history of allergic conjunctivitis. Those who satisfied other inclusion and exclusion criteria and who responded with sufficient itching and hyperemia reactions to screening Ora-CAC® challenges were enrolled. The study was conducted in five visits over a 6- to 9-week period. Key inclusion criteria also included that all subjects had to demonstrate a positive skin test to Japanese cedar pollen-specific allergen at initial screening (Visit 1), have a positive bilateral adverse environment test response (ocular itching score ≥ 2.0 and ocular hyperemia score ≥ 2.0 in the conjunctival vessel bed) within 10 min of instillation of the last titration dose of allergen at Visit 2, have a positive bilateral adverse environment test response of ocular itching ≥ 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 ≥ 2.0 in the conjunctival vessel bed for at least 2 of the 3 time points at Visit 3, have best-corrected visual acuity of ≥ 0.2 in each eye at Visit 1, be willing to discontinue wearing any contact lenses during the study period, starting at least 5 days prior to Visit 2 through Visit 5, and provide written informed consent. Key exclusion criteria included a history of allergic hypersensitivity or known hypersensitivity to any compound or chemical class related to the investigational drug or its excipients, previous participation in a clinical study with Alcaftadine, presence of signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 2, 3, or 4, a history of vernal keratoconjunctivitis and/or atopic keratoconjunctivitis, presence of an active ocular infection, preauricular lymphadenopathy, or history of an ocular herpetic infection, use of disallowed medications during the washout period or anticipated use during the study, use of depot corticosteroids within 6 months before Visit 2 or anticipated use during the study, undergone an ocular surgical intervention within 6 months prior to Visit 1, have any uncontrolled systemic disease, or have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or confound study results.

The study design is shown in Figure 1. At visit 2, escalating concentrations of Japanese cedar pollen were instilled

bilaterally into the conjunctival cul-de-sac of potential subjects. Subject responses were scored for itch and conjunctival hyperemia. After 10 min, a higher allergen dose was instilled, and the process was repeated until a positive reaction was elicited (i.e., when both itching and conjunctival hyperemia scores reached ≥ 2.0 bilaterally). Itching severity was graded by subjects (on a 5-point scale; 0–4), conjunctival, ciliary, and episcleral hyperemia was scored by the investigator on a 5-point ocular redness scale (0–4).

At visit 3, the allergen concentration confirmation visit, the bilateral allergen challenge using the final concentration from visit 2 was performed. Subjects rated ocular itching at 3, 5, 7, and 15 min and scored eyelid swelling and tearing at 7, 15, and 20 min following the 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 a conjunctival hyperemia score ≥ 2 at two of the three time points (7, 15, and 20 min) continued to the treatment visits.

Subjects were enrolled and randomized at visit 3 in a ratio of 1:1:1:1:1 into 5 treatment groups:

- 0.25% Alcaftadine 0.25% bilateral
- 0.1% Olopatadine bilateral
- Vehicle of Alcaftadine 0.25% bilateral
- 0.25% Alcaftadine 0.25%/0.1% Olopatadine contralateral
- 0.25% Alcaftadine 0.25%/Vehicle of Alcaftadine 0.25% contralateral

In each treatment group, subjects were further randomized 1:1 based on the order of Ora-CAC® challenge: 4-h challenge at visit 4 and 16-h challenge at visit 5, or 16-h challenge at visit 4 and 4-h challenge at visit 5 (Figure 1). Randomization was also 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 .

Treatment Visits

At visit 4, randomized subjects received one drop of either Alcaftadine 0.25% ophthalmic solution bilaterally, Olopatadine 0.1% ophthalmic solution¹⁴ bilaterally, vehicle (Alcaftadine ophthalmic solution vehicle) bilaterally, Alcaftadine 0.25%/

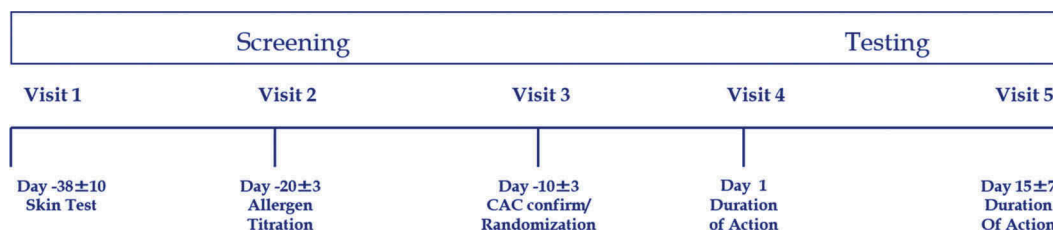


Figure 1. Study design. The study included three screening visits and two treatment visits. At visit 4, subjects with confirmed positive Ora-CAC® challenge¹⁹ to Japanese cedar pollen were randomized to receive study medication, and to 4-h Ora-CAC® challenge at visit 4 followed by 16-h Ora-CAC® at visit 5 or 16-h Ora-CAC® challenge at visit 4 followed by 4-h Ora-CAC® challenge at visit 5.

Olopatadine 0.1% contralaterally, or Alcaftadine 0.25%/vehicle treatment contralaterally. Test agent instillation was conducted by clinic staff.

The primary efficacy measure was ocular itching score quantified by the subject at 5 min post Ora-CAC® challenge in each eye. The secondary efficacy measure was conjunctival hyperemia assessed by the investigator at 15 min post challenge in each eye. Additionally, ocular itching scores at 3, 7, and 15 min post challenge, and conjunctival hyperemia at 7 and 20 min post challenge were recorded. Other secondary endpoints include ciliary and episcleral hyperemia, 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 20.1. Other safety measures included biomicroscopy, fundoscopy, and visual acuity.

Statistical Analysis

Study populations included intent-to-treat (ITT), per protocol (PP), and safety. The ITT population, consisted of all randomized patients, and was used for analyses of efficacy data based on the assigned treatment. The safety population consisted of all treated patients and was used for analyses of all safety data based on the actual treatment received. The PP population consisted of the subset of the ITT population with no protocol deviations affecting the primary efficacy analyses. The PP population was determined prior to database lock and was used to support the primary efficacy analyses.

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 co-primary efficacy analyses were evaluated: (1) superiority of Alcaftadine 0.25% over vehicle in ocular itching at 5 min post Ora-CAC® challenge, challenged 16 h post-dose; and (2) non-inferiority of Alcaftadine 0.25% in ocular itching at 5 min post adverse environment test, challenged 16 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 non-inferiority, 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 non-inferior to Olopatadine 0.1% if the upper limit of the 95% CI did not exceed 0.5 units. If Alcaftadine 0.25% was non-inferior to Olopatadine 0.1% and achieved lower ocular itching score than Olopatadine 0.1%, a test of superiority comparing Alcaftadine 0.25% with challenge 16 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 non-inferiority compared to 0.1% Olopatadine must be demonstrated for the study to be considered positive, no adjustment for multiplicity was used 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 non-inferiority 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, incidence rates of treatment-emergent adverse events (TEAEs) regardless of causality, treatment-related TEAEs, and serious adverse events were assessed on all randomized subjects who received at least one dose of study treatment and were summarized for each treatment group.

Results

Subject Disposition and Demographics

A total of 647 subjects were screened, 263 subjects (140 males, 123 females) were enrolled in the study, and 224 completed the trial. Subject demographics and characteristics were similar between randomized groups (Table 1). Of the 263 subjects randomized, 39 (14.8%) discontinued during the course of the study (30 subjects withdrew consent, three were withdrawn due to protocol violations, two were lost to follow up, one was other reason). Three subjects discontinued study drug due to adverse events classified as chronic fatigue syndrome, primary left spontaneous pneumothorax, and dizziness. None of these were considered related to study drug. Table 1 data also show how subjects were randomized, in part, based upon the degree of their allergic disease severity.

Efficacy Results

Analyses of efficacy were based upon comparisons of treatment groups: Alcaftadine 0.25%-treated eyes challenged 16 h post-dosing ($n = 183$), Olopatadine 0.1%-treated eyes challenged 4 h post dosing ($n = 144$), and vehicle-treated eyes ($n = 138$). Ocular itching scores at screening visits 2 and 3, where no active agent was instilled, were comparable between treatment groups. The primary endpoint, ocular itching score in Alcaftadine-treated eyes at 5 min post Ora-CAC® challenge, challenged 16 h post-dosing was significantly lower than ocular itching score in vehicle-treated eyes (mean difference, 0.98; Table 2) based upon Wilcoxon rank-sum test, demonstrating superiority of Alcaftadine over vehicle ($p < .001$; Table 2). Alcaftadine 0.25%-treated eyes also demonstrated significant reductions in ocular itch scores versus vehicle-treated eyes at all other post challenge time points (3, 7, and 15 min) ($p < .001$; Table 2). At 4 h post-dose, ocular itching scores were also statistically significantly lower in Alcaftadine-treated eyes than in vehicle-treated eyes ($p < .001$) at all post challenge time points (3, 5, 7, and 15 min).

In a second comparison, itch scores 5 min post Ora-CAC® challenge in Alcaftadine 0.25%-treated eyes challenged 16 h post-dose were compared to Olopatadine 0.1%-treated eyes challenged 4 h post-dose (Table 2). The upper limit of the 95% CI for the treatment difference (95% CI: $-0.15, 0.05$) was below 0.5, demonstrating that Alcaftadine 0.25% 16 h post-dose was non-inferior to Olopatadine 0.1% 4 h post-dose.

Table 1. Subject demographics.

	Treatment randomization group					Total N = 263	P value ^a
	Alcaftadine/ Alcaftadine N = 53	Vehicle/Vehicle N = 52	Olopatadine/ Olopatadine N = 53	Alcaftadine/ Vehicle N = 52	Alcaftadine/ Olopatadine N = 53		
Age							
Mean (SD)	38.1 (11.82)	41.7 (13.14)	41.3 (13.44)	40.9 (12.19)	40.6(13.04)	40.5 (12.71)	0.629
Gender							
Male	27 (50.9%)	25 (48.1%)	31 (58.5%)	23 (44.2%)	34 (64.2%)	140 (53.2%)	0.241
Female	26 (49.1%)	27 (51.9%)	22 (41.5%)	29 (55.8%)	19 (35.8%)	123 (46.8%)	
Itch score in Visit 3^b							
≥ 2 and 3 <	32 (60.4%)	32 (61.5%)	31 (58.5%)	31 (59.6%)	32 (60.4%)	158 (60.1%)	0.999
≥ 3	21 (39.6%)	20 (38.5%)	22 (41.5%)	21 (40.4%)	21 (39.6%)	105 (39.9%)	

SD, standard deviation.

^ap-Values based on ANOVA for Age and Pearson's chi-square test or Fisher's exact test for gender or ocular itching score.^bScores for Visit 3 screening evaluated 5 min after Ora-CAC® challenge for the eye with higher score.**Table 2.** Treatment differences in ocular itch (primary variable) and conjunctival hyperemia (secondary variable) scores post Ora-CAC® challenge, after treatment instillation during study visits 4 and 5 (intent-to-treat population; n = number of eyes treated).^a

Time point Post CAC	Alcaftadine 0.25% (n = 183)	Vehicle (n = 138)	Olopatadine 0.1% (n = 144)	Treatment difference (95% CI)	
				Alcaftadine vs. vehicle	Alcaftadine vs. olopatadine
Ocular itching, min, mean (SD)					
3	0.12 (0.305)	0.94 (0.904)	0.18 (0.394)	-0.50 (-0.50, -0.50) <i>p</i> < .001	0.00 (-0.00, 0.00) <i>P</i> = .248
5	0.25 (0.412)	1.25 (0.865)	0.32 (0.538)	-1.00 (-1.00, -1.00) <i>P</i> < .001	0.00 (0.00, 0.00) <i>P</i> = .504
7	0.39 (0.535)	1.37 (0.818)	0.47 (0.590)	-1.00 (-1.00, -1.00) <i>P</i> < .001	0.00 (0.000.00) <i>P</i> = .217
15	0.48(0.610)	1.23(0.815)	0.58 (0.700)	-0.50 (-1.00, -0.50) <i>P</i> < .001	0.00 (0.00, 0.00) <i>P</i> = .282
Conjunctival hyperemia, min, mean (SD)					
7	0.41 (0.618)	0.71 (0.653)	0.69 (0.664)	-0.50 (-0.50, 0.00) <i>p</i> < .001	-0.50 (-0.50, 0.00) <i>p</i> < .001
15	0.84 (0.841)	1.08 (0.789)	1.19 (0.847)	-0.50 (-0.50, 0.00) <i>p</i> = .002	-0.50 (-0.50, 0.00) <i>p</i> < .001
20	1.04(0.940)	1.24 (0.878)	1.46 (0.892)	0.00 (-0.50, 0.00) <i>p</i> = .024	-0.50 (-0.50, 0.00) <i>p</i> < .001

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

^aAllergen challenge with cedar pollen 16 h after alcaftadine 0.25% and vehicle treatment, and 4 h after olopatadine 0.1% treatment.^bp-Values based on the Wilcoxon rank-sum test.^cPoint estimate by Hodges-Lehmann method and 95% confidence interval on both sides.

Ocular itching in Alcaftadine 0.25%-treated eyes was non-inferior to Olopatadine 0.1%-treated eyes at all time points assessed post-challenge (Table 2).

For secondary endpoints a similar statistical comparison was conducted: the conjunctival hyperemia score in Alcaftadine-treated eyes at 15 min post Ora-CAC® challenge, challenged 16 h post-dosing was significantly lower than ocular hyperemia score in vehicle-treated eyes (mean difference, 0.32; Table 2) based upon Wilcoxon rank-sum test, demonstrating superiority of Alcaftadine over vehicle (*p* < .001). Alcaftadine 0.25%-treated eyes also demonstrated significant reductions in conjunctival hyperemia scores versus vehicle-treated eyes at all other post challenge time points (7 and 20 min; *p* < .001 and *p* < .001; Table 2). Conjunctival hyperemia scores were also compared between Alcaftadine 0.25%-treated eyes challenged 16 h post-dose and Olopatadine 0.1%-treated eyes challenged 4 h post-dose (Table 2). Alcaftadine 0.25% demonstrated non-inferiority and statistical superiority to Olopatadine 0.1% at 7 min, 15 min and 20 min post-challenge (*p* < .01 at 7, 15, 20 min; Table 2).

Safety

Overall, adverse events (AEs) were infrequent and mild in severity. Ocular AEs were reported in 25 eyes distributed among the 3 active agent treatments (Table 3). The most common ocular AE reported was punctate keratitis (n = 12), with the majority (n = 8) of these occurring in 0.1%

Olopatadine-treated eyes. A total of 27 non-ocular AEs were reported and were evenly distributed between the 5 randomization groups. No event was reported more than twice and the most common AEs are listed in Table 4. No deaths or other serious adverse events were reported in the course of this study. No subject discontinued the study due to an ocular AE.

Discussion

Allergic conjunctivitis is common in Japan, most often associated with exposure to Japanese cedar pollen.⁵ In this study, we examined the duration of action for an antihistamine

Table 3. Ocular adverse events by active agent.

MedDRA term	Alcaftadine 0.25% N = 190 ^a	Vehicle N = 144	Olopatadine N = 148
Total ocular AEs	8 (4.2%)	6 (4.2%)	11 (7.4%)
Punctate keratitis	3 (1.6%)	1 (0.7%)	8 (5.4%)
Eye pruritus	2 (1.1%)	2 (1.4%)	0 (0.0%)
Conjunctival hyperemia	2 (1.1%)	1 (0.7%)	2 (1.4%)
Asthenopia	2 (1.1%)	1 (0.7%)	0 (0.0%)
Retinal hemorrhage	2 (1.1%)	0 (0.0%)	0 (0.0%)
Ocular discomfort	2 (1.1%)	0 (0.0%)	0 (0.0%)
Conjunctival follicles	1 (0.5%)	1 (0.7%)	0 (0.0%)
Eyelid edema	0 (0.0%)	2 (1.4%)	0 (0.0%)
Optic disc hemorrhage	0 (0.0%)	0 (0.0%)	1 (0.7%)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

^aN represents the number of eyes treated. Percentages are calculated using the number of eyes experiencing a treatment-emergent adverse event. MedDRA Dictionary (version 20.1) is used for coding.

Table 4. Non-ocular adverse events by treatment group.^a

	Alcaftadine 0.25%/ Alcaftadine 0.25% N = 46	Vehicle/ Vehicle N = 48	Olopatadine/ Olopatadine N = 49	Alcaftadine 0.25%/ Vehicle N = 48	Alcaftadine 0.25%/ Olopatadine\ N = 50
Total events	7 (15.2%)	3 (6.3%)	6 (12.2%)	5 (10.4%)	6 (12.0%)
Neck pain	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Back pain	0 (0.0%)	1 (2.1%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (2.1%)	0 (0.0%)
Headache	0 (0.0%)	0 (0.0%)	2 (4.1%)	0 (0.0%)	0 (0.0%)
Rhinorrhea	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	2 (4.0%)

^aIncludes all AEs with a frequency >1.

currently unavailable to Japanese patients with AC. The study focused on evaluation of the duration of efficacy and safety of Alcaftadine 0.25% ophthalmic solution as a preventive treatment for cedar pollen-related allergic conjunctivitis. The study was conducted using the Ora-CAC[®] model, a clinical approach with an established record of accurately predicting therapeutic efficacy in real-world conditions, previously developed and published for studying allergic conjunctivitis in a clinical setting.²⁰

In a previous study, we established that Alcaftadine 0.25% was superior to vehicle in preventing both itching and conjunctival hyperemia when dosed 8 h prior to allergen challenge, and was non-inferior to Olopatadine 0.1% dosed 4 h prior to allergen challenge in preventing ocular itching and conjunctival hyperemia.¹⁸ In the study presented here, our aim was to extend this comparison to Alcaftadine 0.25% efficacy 16 hours post-dosing, a time frame consistent with once-daily dosing regimens. Similar protocols were employed in both the previous and current studies. In this extended study, Alcaftadine 0.25% once again provided significant itch relief versus vehicle 16 hours after dosing. In addition, Alcaftadine 0.25% dosed 16 hours prior to challenge was non-inferior to Olopatadine 0.1% dosed 4 hours before challenge in reducing ocular itching. Alcaftadine also demonstrated significant relief of conjunctival hyperemia versus vehicle. Alcaftadine was non-inferior to Olopatadine dosed 4 hours prior to challenge, which is the on label use for Olopatadine 0.1% in Japan. Of note, Alcaftadine dosed 16 hours before challenge was statistically superior to Olopatadine dosed 4 hours prior to challenge at reducing conjunctival hyperemia. This indicates Alcaftadine provides extended protection against allergic conjunctivitis. Alcaftadine 0.25% was well tolerated with a similar safety profile to that described in previous studies.^{12,21,22}

Previous studies compared once-daily treatment with Alcaftadine 0.25% with Olopatadine 0.2%, a formulation also approved for once-daily dosing in the USA. In these studies, the two treatments were comparable over most time points, although Alcaftadine efficacy on itch was numerically greater at the 16-h post-dosing challenges.^{21,22} Among ocular anti-histamines, Alcaftadine is unique in that it exhibits antagonistic activity against H1 and H2 receptors, as well as H4 receptors.^{10,11,23,24} Alcaftadine 0.25% has shown an earlier onset of action than Olopatadine 0.1%, achieving lower itching scores 3 min post Ora-CAC[®] challenge at 15 min post treatment, and a sustained duration of action up to 24 h post treatment.^{12,21,22,25} There is also evidence that Alcaftadine has an anti-inflammatory effect, reducing eosinophil recruitment and maintaining stability of the epithelial junctional protein,

zonula occludens-1, as demonstrated in a murine model of allergic conjunctivitis.¹⁶ Further, Alcaftadine demonstrated superiority over Olopatadine in the maintenance of epithelial gap junctions, which may lead to the more sustained duration of Alcaftadine compared to Olopatadine.¹⁶

In the current study, Alcaftadine 0.25% dosed 16 h prior to allergen challenge was found to be as effective or superior to Olopatadine 0.1% dosed 4 h prior to allergen challenge in preventing signs and symptoms of Japanese cedar-pollen allergic conjunctivitis. Overall, this study demonstrates the safety and efficacy for the once-daily use of Alcaftadine 0.25% for the prevention of signs and symptoms associated with allergic conjunctivitis triggered by Japanese cedar pollen.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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