U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206276
Supplement #:	0000
Drug Name:	Olopatadine Hydrochloride Ophthalmic Solution 0.77%
Indication(s):	Treatment of Itching Associated with Allergic Conjunctivitis
Applicant:	Alcon
Date(s):	Submitted: 07/30/2014 PDUFA date: 01/30/2015
Review Priority:	Priority
Biometrics Division:	DBIV
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Keywords: itching, redness, allergic conjunctivitis, superiority

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1 EXECUTIVE SUMMARY

The applicant (Alcon) seeks approval of Olopatadine Hydrochloride Ophthalmic Solution, 0.77% (Olopatadine HCI Solution, 0.77%, also referred to as Olopatadine 0.77% throughout this review) for the treatment of ocular itching associated with allergic conjunctivitis. In 1996, Olopatadine HCI Solution 0.1% (PATANOL®) was approved for **twice daily** dosing in the U.S for the treatment of the signs and symptoms of allergic conjunctivitis. A higher concentration formulation, Olopatadine HCI Solution 0.2% (PATADAY®) was also approved for dosing **once per day** in the U.S. for the treatment of ocular itching (**but not redness**) associated with allergic conjunctivitis since 2004. This submission is for a new formulation of olopatadine having a 0.77% concentration of the active ingredient, olopatadine hydrochloride for dosing **once daily**. By increasing the concentration of olopatadine hydrochloride to 0.77%, the applicant intended to demonstrate that the new formulation would extend the benefit offered by Olopatadine, 0.2% (PATADAY®) while maintaining its safety. In order to support the approval of this new formulation, the applicant submitted two pivotal efficacy studies: Study C-10-126, and Study C-12-053.

Studies C-10-126 and C-12-053 were similarly designed phase 3 studies. Both were multicenter, randomized, double-masked, active and vehicle controlled, parallel-group studies and used the conjunctival allergen challenge (CAC) model to evaluate the safety and efficacy of Olopatadine 0.77% versus Vehicle or active comparators in the treatment of ocular itching associated with allergic conjunctivitis. Both studies were conducted in patients at least 18 years of age with a history of seasonal and/or perennial allergic conjunctivitis for at least 1 year prior to study entry and a positive allergic skin test within 24 months prior to study entry. Study C-10-126 had PATADAY and Vehicle as comparators. Study C-12-053 had PATADAY, PATANOL and Vehicle as comparators; however, PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (the day before the 24-hour duration-of-action efficacy evaluation) and Visit 4.

The primary efficacy variable for both studies was patient-evaluated ocular itching severity scores (assessed using a 0-4 scale with 0.5 unit increments: 0 = none, 4 = incapacitating itch). In Study C-10-126, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visits 4B (16-hour duration-of-action) and 5 (onset-of-action). In Study C-12-053, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visit 3B (24-hour duration-of-action) and Visit 4 (onset-of-action).

The primary efficacy objectives for Study C-10-126 were to demonstrate the superiority of Olopatadine 0.77% compared to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at:

- Onset-of-action
- 16-hour duration-of-action

A secondary efficacy objective in this study was to (b) (4)

The primary efficacy objectives for Study C-12-053 were to demonstrate the superiority of Olopatadine 0.77% for the treatment of ocular itching compared to:

- Vehicle at the onset-of-action;
- Vehicle at 24-hour duration-of-action;
- (b) (4)
- PATADAY at 24-hour duration-of-action.

Both studies used the intention-to-treat (ITT) set in the primary efficacy analysis, which included all randomized patients who received study medication. Patients were included in the ITT analysis set according to randomized treatment.

In Study C-10-126, a total of 202 patients from three centers in the U.S. were randomized to the three treatment groups respectively: 66 in Olopatadine HCl Solution 0.77% group, 68 in PATADAY group, and 68 in Vehicle group. Sixteen patients discontinued leaving 186 (92.1%) patients completing the study.

In Study C-12-053, a total of 345 patients from six centers in the U.S. were randomized to the four treatment groups respectively: 98 in Olopatadine HCl Solution 0.77% group, 99 in PATADAY group, 99 in PATNOL group, and 49 in Vehicle group. A total of 325 (94.2%) patients completed the study.

Based on the efficacy results (Table 1):

- In both Study C-10-126 and Study C-12-053, Olopatadine 0.77% was superior to Vehicle for treating ocular itching associated with allergic conjunctivitis at onset-of-action, and 24-hour duration-of-action.
- In Study C-10-126, at 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. In Study C-12-053, Olopatadine 0.77% was superior to PATADAY for ocular itching associated with allergic conjunctivitis at 24-hour duration-of-action at 2 (3 and 5 minutes) out of 3 post CAC time points. The point estimate for the treatment difference at 7 minutes post-CAC was in favor of Olopatadine 0.77% but did not demonstrate statistical significance.

Although in Study C-12-053, (b) (4), the efficacy results were consistent between Study C-12-053 and Study C-10-126 and all in favor of Olopatadine 0.77%. In addition, in both studies, comparing with Vehicle, the ocular itching treatment effects of Olopatadine 0.77% were highly significant (p-value<0.0001) at all three time points in the efficacy evaluation visits. Therefore, this reviewer concluded that there is enough evidence to support the efficacy of Olopatadine 0.77% for the treatment of ocular itching associated with allergic conjunctivitis and recommended its approval for this indication.

The approved regimen for PATANOL was twice daily; however, in Study C-12-053, PATANOL was dosed only once (instead of the approved twice-a-day regimen) at each study visit day. (b) (4)

(b) (4)

Table 1: Analysis of Ocular Itching Scores* for Studies C-10-126 and C-12-053 (ITT)

	Time Point	Olopatadine, 0.77%	PATADAY (Olopatadine, 0.2%)		PATANOL Dosed Once[1] (Olopatadine, 0.1%)		Vehicle	
C-10-126		(N = 66)	(N = 68)				(N = 68)	
		Mean	Mean	Difference (95% CI)	Mean	Difference (95% CI)	Mean	Difference (95% CI)
Onset	Average	0.46	0.54	-0.08 (-0.37, 0.21)			1.98	-1.51 (-1.81, -1.23)
	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)			1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)			2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)			1.97	-1.49 (-1.80, -1.18)
16h	Average	0.75	0.96	-0.21 (-0.49, 0.07)			2.20	-1.45 (-1.73, -1.17)
	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)			2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)			2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)			2.13	-1.38 (-1.69, -1.07)
24h	Average	1.04	1.48	-0.44 (-0.72, -0.16)			2.55	-1.51 (-1.79, -1.24)
	3 mins	0.93	1.41	-0.48 (-0.76, -0.20)			2.54	-1.61 (-1.88, -1.33)
	5 mins	1.10	1.52	-0.42 (-0.72, -0.12)			2.62	-1.51 (-1.81, -1.21)
	7 mins	1.09	1.50	-0.41 (-0.72, -0.10)			2.50	-1.41 (-1.72, -1.11)
C-12-053		(N = 98)	(N = 99)		(N = 99)		(N = 49)	
Onset	Average	0.52	0.56	-0.05 (-0.24, 0.14)	(b) (4)		1.91	-1.39 (-1.62, -1.16)
	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)			1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)			1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)			1.82	-1.17 (-1.45, -0.90)
24h	Average	1.16	1.40	-0.24 (-0.48, -0.00)			2.27	-1.11 (-1.40, -0.82)
	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)			2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)			2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)			2.14	-0.89 (-1.22, -0.57)

* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.

[1] PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action).

Source: Tables 2.7.3.2-2, 2.7.3.2-3, 2.7.3.2-7, 2.7.3.2-10, and 2.7.3.2-11 of Summary of Clinical Efficacy.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Olopatadine is an anti-allergic agent that exerts its effects through multiple different mechanisms of action, including selective antagonism of histamine H1 receptors, mast cell stabilization, and prevention of histamine induced inflammatory cytokine production by human conjunctival epithelial cells. Olopatadine is used in several prescription products around the world as a topical ocular eye drop, a topical nasal spray and as an oral medication.

Allergic conjunctivitis is inflammation of the conjunctiva (the membrane covering the white part of the eye) due to allergy. Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common forms of allergic conjunctivitis and are caused by an IgE-mediated reaction to allergens such as grass, weed and tree pollens, dust mites, animal dander and molds. Signs and symptoms of allergic conjunctivitis include ocular itching, ocular redness, tearing, eyelid swelling and chemosis. The symptoms are due to release of histamine and other active substances by mast cells, which stimulate dilation of blood vessels, irritate nerve endings, and increase secretion of tears. Treatment of allergic conjunctivitis is by avoiding the allergen (e.g., avoiding grass in bloom during "hay fever season") and treatment with antihistamines, either topical (in the form of eye drops), or systemic (in the form of tablets).

2.1.2 History of Drug Development

Olopatadine is used in several prescription products around the world as a topical ocular eye drop, a topical nasal spray and as an oral medication. In 1996, PATANOL® (Olopatadine Hydrochloride Ophthalmic Solution 0.1%) was approved for **twice daily** dosing in the U.S for the treatment of the signs and symptoms of allergic conjunctivitis (both itching and redness). A higher concentration formulation, PATADAY® (Olopatadine Hydrochloride Ophthalmic Solution 0.2%) is also approved for dosing **once per day** in the U.S. for the treatment of ocular itching (**but not redness**) associated with allergic conjunctivitis since 2004.

According to the applicant, as the aqueous solubility of olopatadine at neutral pH is a limiting factor in formulating olopatadine-containing ophthalmic solutions, a new formulation was developed to overcome this limitation. By increasing the concentration of olopatadine hydrochloride to 0.77%, the applicant wanted to demonstrate that the new formulation would extend the benefit offered by Olopatadine, 0.2% (PATADAY®) while maintaining its safety.

The Phase 3 study protocols and analysis plans for the test product were submitted and reviewed under IND 60991.

During the pre-NDA meeting between the Agency and the applicant on 08/26/2013, regarding the applicant's question of whether the Agency agree that inclusion of the comparative efficacy results in the package insert, the Agency's response was:

> *"The inclusion of two active control safety and efficacy studies which compare Olopatadine 0.77% and Pataday, as long as each study shows superiority over the active comparator(s) with appropriate multiplicity adjustment to control the overall Type I error rate, may allow comparative efficacy labeling claims."*

In addition, regarding the on-going Study C-12-053 at that time, the statistical reviewer had the following review comment:

> *"According to your statistical analysis plan (SAP), the success criterion for this study is that all co-primary hypotheses must be rejected at the 5% level; otherwise, the study would be considered as failure. However, if you also intent to claim the study to be successful when the test product is shown to be superior to the vehicle but not superior to the active controls, the protocol needs to address multiplicity issue due to having multiple pathways of claiming study success. To address this issue, we recommend you consider to use the Bonferroni correction or the following gatekeeping sequential testing approach:*
>
> - ***Step 1****: first test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at the onset of action using a significant level of 5% (2-sided). If the test is statistically significant, proceed to Step 2; otherwise no testing will be performed for the remaining three hypotheses.*
> - ***Step 2****: test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at 24 hours duration of action using a significant level of 5% (2-sided). If the test is statistically significant, proceed to Step 3; otherwise no testing will be performed for the remaining two hypotheses.*
> - ***Step 3****: test the treatment difference in the itching score between Olopatadine 0.77% and PATANOL at 24 hours duration of action using a significant level of 5% (2-sided). If the test is statistically significant, proceed to Step 4; otherwise no testing will be performed for the remaining hypothesis.*
> - ***Step 4****: test the treatment difference in the itching score between Olopatadine 0.77% and PATADAY at 24 hours duration of action using a significant level of 5% (2-sided)."*

However, the applicant did not follow our recommendation and still proceeded with the success criterion for Study C-12-053 being that all four primary hypotheses must be rejected at the 5% level simultaneously.

2.1.3 Studies Reviewed

Olopatadine 0.77% clinical development plan included five clinical studies: two Phase 1 studies (Study C-10-127 and C-11-036), two pivotal Phase 3 safety and efficacy studies (Studies C-10-126 and C-12-053), and a six-week safety study (C-12-028).

Study C-10-127 was a Phase 1, single center, randomized, double-masked, vehicle and active controlled, three-way crossover study conducted in healthy subjects 18 years of age or older to evaluate the comfort and safety of Olopatadine HCl Solution, 0.77%. This study is not included in the statistical review for this NDA.

C-11-036 was a single center, randomized, double-masked, vehicle controlled, parallel-group safety and PK study conducted in healthy, adult, Japanese (at least 50%) and non-Japanese subjects. This study is not included in the statistical review for this NDA either.

Study C-12-028, was a Phase 3, six week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study evaluating the safety of Olopatadine HCl Solution, 0.77% compared to Vehicle when administered once daily in both eyes for 6 weeks. Healthy subjects at least 2 years of age or older with asymptomatic eyes were randomized in a 2:1 ratio to Olopatadine HCl Solution, 0.77% or Vehicle respectively. Subjects younger than 6 years of age were randomized from 1 randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule. All randomized subjects received 1 drop of either Olopatadine HCl Solution, 0.77% or Vehicle once daily in both eyes for 6 weeks. The safety data from this study is included in the statistical review for this NDA.

This statistical review focused on the two pivotal Phase 3 safety and efficacy studies: Studies C-10-126 and C-12-053. Key information of these two studies and the safety study C-12-028 is presented in the following table.

Table 2: Key Information for Studies C-10-126 and C-12-053

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
C-10-126	*Phase 3 randomized double masked active and vehicle control*	*One drop per eye at each study visit (Visit 3A [Day 0], Visit 4A [Day 14], and Visit 5 [Day 21])*	*n/a*	*Vehicle – 68 subjects Olopatadine 0.77% – 66 subjects Olopatadine 0.2% – 68 subjects*	*Adult patients (≥ 18 years of age) with seasonal or perennial allergic conjunctivitis*
C-12-053	*Phase 3 randomized double masked active and vehicle control*	*One drop per eye at each study visit (Visit 3A [Day 0], and Visit 4 [Day 14])*	*n/a*	*Vehicle – 49 Olopatadine 0.77% – 98 Olopatadine 0.2% (PATADAY) – 99 Olopatadine 0.1% (PATANOL) – 99*	*Adult patients (≥ 18 years of age) with seasonal or perennial allergic conjunctivitis*
C-12-028 (6-Week Safety)	*Randomized Double Masked*	*6 weeks on test or control article*		*Vehicle – 169 subjects Olopatadine*	*Safety relative to vehicle*

	Parallel Group			*0.77% – 330 subjects*	

Source: Table 2.7.3.1-1 of Summary of Clinical Efficacy.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies C-10-126, and C-12-053. The study reports are available at: \\Cdsesub1\evsprod\NDA206276\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ocular-itching\5351-stud-rep-contr.

The applicant submitted SAS datasets and program codes that were used to generate the study reports electronically; they are available at: \\Cdsesub1\evsprod\NDA206276\0000\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary and key secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The statistical analysis plans (SAPs) for the two pivotal studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies C-10-126 and C-12-053 were two similarly designed phase 3 pivotal studies. Both studies were multicenter, randomized, double-masked, both active and vehicle controlled, parallel-group studies and used the conjunctival allergen challenge (CAC) model. The objective of these studies was to demonstrate the efficacy and safety of Olopatadine HCl Solution, 0.77% in patients with seasonal or perennial allergic conjunctivitis. A side by side comparison of the design elements of studies C-10-126 and C-12-053 is presented in the following table.

Table 3: Side by Side Comparison of the Design Elements of Studies C-10-126 and C-12-053

Study	**C-10-126**	**C-12-053**
Design	Phase 3, multi-Center, randomized, double-masked, parallel-group, vehicle and active controlled, efficacy and safety study	Phase 3, multi-Center, randomized, double-masked, parallel-group, vehicle and active controlled, efficacy and safety study
Indication	Allergic conjunctivitis	Allergic conjunctivitis
Treatment Arms	Vehicle Olopatadine 0.77% Olopatadine 0.2% (PATADAY)	Vehicle Olopatadine 0.77% Olopatadine 0.2% (PATADAY) Olopatadine 0.1% (PATANOL)

Treatment Regimen	1 dose (1 drop per eye) at each of Visits 3A, 4A and 5	1 dose (1 drop per eye) at each of Visits 3A and 4
Randomization	1:1:1	1:2:2:2
No of Sites	3 sites in US	6 sites in US
No of Patients	Vehicle – 68 subjects Olopatadine 0.77% – 66 subjects Olopatadine 0.2% – 68 subjects	Vehicle – 49 Olopatadine 0.77% – 98 Olopatadine 0.2% (PATADAY) – 99 Olopatadine 0.1% (PATANOL) – 99
Study Population	Adult patients with history of allergic conjunctivitis	Adult patients with history of allergic conjunctivitis
Visits	7 Visits: Visit 1 (Day -21) – Screening Visit 2 (Day -14) – Confirmation CAC Visit 3A (Day 0) – Randomization Visit 3B (Day 1) – 24-hour duration CAC visit Visit 4A (Day 14) Visit 4B (Day 14 + 16 Hours) – 16-hour duration CAC visit Visit 5 (Day 21) – Onset-of-action CAC visit	5 Visits: Visit 1 (Day -21) – Screening Visit 2 (Day -14) – Confirmation CAC Visit 3A (Day 0) – Randomization Visit 3B (Day 1) – 24-hour duration CAC visit Visit 4 (Day 14) – Onset-of-action CAC visit

Source: Statistical Reviewer's Summary.

Both studies were conducted in patients at least 18 years of age with a history of seasonal and/or perennial allergic conjunctivitis for at least 1 year prior to study entry and a positive allergic skin test within 24 months prior to study entry. C-10-126 had PATADAY (Olopatadine HCI, 0.2%) and Vehicle as comparators, C-12-053 had PATADAY, PATANOL (Olopatadine HCI, 0.1%) and Vehicle as comparators. The randomization ratio in C-10-126 was 1:1:1 (Oloptadine HCl Solution, 0.77%: PATADAY: Vehicle) and in C-12-053, it was 2:2:2:1 (Oloptadine HCl Solution, 0.77%: PATADAY: PATANOL: Vehicle). Patients were evaluated for safety and efficacy during the visits conducted at

- Visit 1 (Day -21 ± 2 days; Screening – Titration CAC)
- Visit 2 (Day -14 ± 3 days; Confirmation CAC)
- Visit 3A (Day 0; Randomization & Test Article [TA] instillation)
- Visit 3B (Day 1; CAC 24 hours post TA instillation);
- For Study C-12-053:
    - Visit 4 (Day 14 ± 2 days; CAC 27 minutes post TA instillation)
- For Study C-10-126:
    - Visit 4A (Day 14 ± 2 days; TA instillation)
    - Visit 4B (on the Day after Visit 4A; CAC 16 hours post TA instillation)
    - and Visit 5 (Day 21 ± 3 days; CAC 27 minutes post TA instillation).

In the DOSAGE and ADMINISTRATION part of the approved label for PATANOL dated April 17th, 2003, it stated "*The recommended dose is one drop in each affected eye two times per day at an interval of 6 to 8 hours.*"

Based on the study protocol for Study C-12-053, in Section 9.2 Usage (Page 405 of Study C-12-053 Study Report), the applicant stated "*Patients will receive 1 dose of the assigned investigational product (Olopatadine HCl Solution, 0.77%, Vehicle, PATADAY or PATANOL) at Visits 3A and 4. A dose is defined as 1 drop per eye of study product instilled topically.*" And in

the study report body, the applicant also mentioned at Section 9.4.5 SELECTION AND TIMING OF DOSE FOR EACH PATIENT (Page 66 of Study C-12-053 Study Report) that "*Randomization occurred at Visit 3A via IRT. Patients received 1 dose of the assigned investigational product at Visits 3A and 4. A dose was defined as 1 drop per eye of study product instilled topically.*"

Therefore, this statistical reviewer concluded that the approved regimen for PATANOL was twice daily; however, in Study C-12-053 that comparing Olopatadine 0.77% with PATANOL at 24-hour duration-of-action, PATANOL was dosed for only once (instead of the approved twice-a-day regimen) in the previous day visit (Visit 3A).

Table 4: Study C-10-126 Schedule of Assessment

	Study Visits							
	Visit 1	Visit 2	Visit 3A	Visit 3B	Visit 4A	Visit 4B	Visit 5	Early Exit Visit
Procedure/ Assessment	Day -21 (± 2 days)	Day -14 (± 3 days)	Day 0	Day 1	Day 14 (± 2 days)	Day after Visit 4A	Day 21 (+ 3 days)	
Informed Consent	X							
Demographics	X							
Medical/Medication History	X							
Allergic Skin Test[1]	X							
Medical/Medication History Update		X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X						X	X
Inclusion/Exclusion	X	X	X					
BCVA[3]	X	X	X	X	X	X	X	X
Slit-Lamp Examination[3]	X	X	X	X	X	X	X	X
IOP Assessment[4]	X						X	X
DFE[4]	X						X	X
Screening Conjunctival Allergen Challenge (CAC)	X	X						
Ocular Allergic Signs and Symptoms Assessments	X	X	X	X[5]	X	X[5]	X[5]	
Randomization			X					
Administer Treatment(s)			X		X		X	
Ocular Discomfort Assessment			X					
Adverse Events (Both Volunteered and Elicited)	X	X	X	X	X	X	X	X
Treatment Efficacy CAC				X[6]		X[7]	X[8]	
Exit							X	X

1 If one has not been done within 24 months prior to Visit 1
2 Females of childbearing potential only
3 Prior to CAC and/or treatment instillation at all visits; also after all post-CAC assessments at Visit 5/Exit
4 After all post-CAC assessments
5 Pre-CAC and 3, 5, 7, 15 and 20 minutes post-CAC (window of +/- 1 min. for each time point)
6 24 hours (+ 1hr) after treatment instillation
7 16 hours (+ 1hr) after treatment instillation
8 27 minutes (+/- 1min) after treatment instillation
Source: Table 9.1.-1 of Study C-10-126 Report.

Table 5: Study C-12-053 Schedule of Assessment

	Study Visits					
	Visit 1	Visit 2	Visit 3A	Visit 3B	Visit 4	Early Exit Visit
Procedure/ Assessment	Day -21 (±2 days)	Day -14 (± 3 days)	Day 0	Day 1	Day 14 (± 2 days)	
Informed Consent	X					
Demographics	X					
Medical/Medication History	X	X	X			
Allergic Skin Test1	X					
Change in Concomitant Medications		X	X	X	X	X
Urine Pregnancy Test2	X				X	X
Inclusion/Exclusion	X	X	X			
BCVA3	X	X	X	X	X	X
Slit-Lamp Biomicroscopy3	X	X	X	X	X	X
IOP Assessment4	X				X	X
DFE4	X				X	X
Screening Conjunctival Allergen Challenge (CAC)	X	X				
Ocular Allergic Signs and Symptoms Assessments	X	X	X5	X6	X7	
Randomization			X			
Administer Treatment(s)			X		X	
Treatment Efficacy CAC				X8	X9	
Ocular Discomfort Assessment			X			
Adverse Events (Both Volunteered and Elicited)	X	X	X	X	X	X
Exit					X	X

1 If has not been done within 24 months prior to Visit 1
2 Females of childbearing potential only
3 Prior to CAC and/or treatment instillation all visits; and after all post-CAC assessments Visit 4/Exit
4 After all post-CAC assessments
5 Pre-dose
6 3, 5, 7, 15 and 20 minutes post-CAC (window of ± 1 min. for each time point)
7 Pre-dose and 3, 5, 7, 15, and 20 minutes post-CAC (window of ± 1 min. for each time point)
8 24 hours (+ 1hr) after treatment instillation
9 27 minutes (± 1min) after treatment instillation
Source: Table 9.1.-1 of Study C-12-053 Report.

The protocol-defined key inclusion criteria were

- Subject needed to have a positive bilateral CAC test response (defined as ≥ 2 itching and ≥ 2 redness in 2 of the 3 vessel beds) at Visit 1 (Screening – Titration CAC visit) within 10 minutes of the last titration challenge

- Subject needed to have a positive bilateral CAC test response (defined as ≥ 2 itching and ≥ 2 redness in 2 of the 3 vessel beds) at Visit 2 (Confirmation CAC visit) in at least 2 of the 3 post-CAC time points.

And the protocol-defined key exclusion criteria were:

- Presence of signs/symptoms of active allergic conjunctivitis (defined as > 1 score for redness in any of the 3 vessel beds and/or any itching) at the start of Visits 1, 2, 3A, 4A, or 5. Patients presenting with signs/symptoms as described above were discontinued from the study.

For both studies, the applicant defined primary endpoint was patient-evaluated ocular itching severity scores. Scores were assessed using a 0-4 scale with 0.5 unit increments:

0 = None
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye
1.0 = An intermittent tickle sensation involving more than just the corner of the eye
1.5 = An intermittent all-over tickling sensation
2.0 = A mild continuous itch (can be localized) without desire to rub
2.5 = A moderate, diffuse continuous itch with desire to rub.
3.0 = A severe itch with desire to rub
3.5 = A severe itch improved with minimal rubbing
4.0 = An incapacitating itch with an irresistible urge to rub

Ocular itching was assessed for both eyes. In Study C-10-126, patients assessed their ocular itching at Visits 4B (16-hour duration-of-action) and 5 (onset-of-action) at pre-CAC and 3, 5, and 7 minutes post-CAC. In Study C-12-053, patients evaluated their ocular itching at Visit 3B (24-hour duration-of-action) and Visit 4 (onset-of-action) at pre-CAC and 3, 5, and 7 minutes post-CAC.

The primary efficacy objectives for Study C-10-126 were to demonstrate the superiority of Olopatadine 0.77% compared to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at:

- Onset-of-action
- 16-hour duration-of-action

The primary efficacy objectives for Study C-12-053 were to demonstrate the superiority of Olopatadine 0.77% for the treatment of ocular itching compared to:

- Vehicle at the onset-of-action;
- Vehicle at 24-hour duration-of-action;
- (b) (4)
- PATADAY at 24-hour duration-of-action.

The secondary objectives for Study C-10-126 were:

- (b) (4) Olopatadine HCl Solution, 0.77% compared to Vehicle for 2 of 3 time points at Visit 5 for the treatment of conjunctival redness associated with allergic conjunctivitis for the onset-of-action.

- [redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to Vehicle for 2 of 3 time points at Visit 4B for the treatment of conjunctival redness associated with allergic conjunctivitis for 16-hour duration-of-action.
- [redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to PATADAY® for 2 of 3 time points at Visit 3B for the treatment of total redness associated with allergic conjunctivitis for 24-hour duration-of-action.
- [redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to PATADAY for 2 of 3 time points at Visit 3B for the treatment of ocular itching associated with allergic conjunctivitis for 24-hour duration-of-action.
- [redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to PATADAY for 2 of 3 time points at Visit 3B for the treatment of conjunctival redness associated with allergic conjunctivitis for 24-hour duration-of-action.

The secondary objectives for Study C-12-053 [redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to PATADAY for the treatment of

- Conjunctival redness associated with allergic conjunctivitis at the onset-of-action (Visit 4);
- Total redness associated with allergic conjunctivitis at the onset-of-action (Visit 4);
- Proportion of ocular itching responders at the 24-hour duration-of-action (Visit 3B);
- Conjunctival redness associated with allergic conjunctivitis at the 24-hour duration-of-action (Visit 3B);
- Total redness associated with allergic conjunctivitis at the 24-hour duration-of-action (Visit 3B);
- Proportion of ocular itching responders at the onset-of-action (Visit 4); and

[redacted] (b) (4) Olopatadine HCl Solution, 0.77% compared to PATANOL for the treatment of

- Conjunctival redness associated with allergic conjunctivitis at the onset-of-action (Visit 4);
- Total redness associated with allergic conjunctivitis at the onset-of-action (Visit 4);
- Proportion of ocular itching responders at the 24-hour duration-of-action (Visit 3B);
- Conjunctival redness associated with allergic conjunctivitis at the 24-hour duration-of-action (Visit 3B);
- Total redness associated with allergic conjunctivitis at the 24-hour duration-of-action (Visit 3B); and
- Proportion of ocular itching responders at the onset-of-action (Visit 4).

The sample size estimation of 64 subjects per arm in Study C-10-126 was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- t-test at the 0.05 two-sided level of significance;
- A mean difference of 1 unit between Olopatadine HCI Solution, 0.77% and Vehicle for ocular itching score;
- A common standard deviation of 1.0;
- 99% power to detect the treatment difference at a single time point.

The sample size estimation of 94 subjects per arm in Study C-12-053 was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- t-test at the 0.05 two-sided level of significance;
- Mean difference of 0.42 units in ocular itching at 24-hour duration-of-action between Olopatadine HCl Solution, 0.77% and PATADAY
- A common standard deviation of 0.88;
- 90% power to detect the treatment difference at a single time point.

According to the applicant, the mean differences and the standard deviations were estimated based on data of previous CAC studies.

3.2.2 Statistical Methodologies

For both studies, the primary efficacy endpoint was patient-evaluated ocular itching severity scores. Scores were assessed using a 0-4 scale with 0.5 unit increments:

0 = None
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye
1.0 = An intermittent tickle sensation involving more than just the corner of the eye
1.5 = An intermittent all-over tickling sensation
2.0 = A mild continuous itch (can be localized) without desire to rub
2.5 = A moderate, diffuse continuous itch with desire to rub.
3.0 = A severe itch with desire to rub
3.5 = A severe itch improved with minimal rubbing
4.0 = An incapacitating itch with an irresistible urge to rub

Ocular itching was assessed for both eyes.

Both studies used the intention-to-treat (ITT) set as the primary efficacy analysis set. The ITT set included all randomized patients who received study medication. Patients were included in the ITT analysis set according to randomized treatment.

The primary efficacy hypotheses for Study C-10-126 were Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at:

- Onset-of-action
- 16-hour duration-of-action

(b) (4)

, the statistical reviewer also examined the efficacy results for the following two hypotheses in Study C-10-126:

- For the treatment of ocular itching, Olopatadine 0.77% was superior to:
  - Vehicle at 24-hour duration-of-action;
  - PATADAY at 24-hour duration-of-action.

The primary efficacy hypotheses for Study C-12-053 were for the treatment of ocular itching, Olopatadine 0.77% was superior to:

- Vehicle at the onset-of-action;
- Vehicle at 24-hour duration-of-action;
- (b) (4)
- PATADAY at 24-hour duration-of-action.

In both studies, the applicant defined all the primary efficacy hypotheses as co-primary hypotheses, which meant that the success criterion for each study was that all co-primary hypotheses must be statistically significant at the 5% level; otherwise, the study would be considered as failure. During the protocol design stage of Study C-12-053, the statistical reviewer reminded the applicant that for Study C-12-053 the success criterion of rejecting four hypotheses simultaneously might be hard to achieve; the statistical reviewer also suggested gatekeeping testing approach that rejected the four hypotheses sequentially as an alternative. However, the applicant still proceeded with the success criterion for Study C-12-053 being that all four primary hypotheses must be rejected at the 5% level simultaneously.

For both studies, at each study visit (onset-of-action and 16/24-hour duration-of-action), the applicant stated that statistical significance was required at 2 out of 3 time points to demonstrate superiority of Olopatadine 0.77% over Vehicle, PATANOL, or PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. However, this approach would not control the overall Type I error rate since there were three different scenarios (b) (4) – the first two time points were statistically significant; the first and third time points were statistically significant; or the second and third time points were statistically significant.

In order to better understand the efficacy results with the overall Type I error for each study being controlled, the statistical reviewer considered the following approach while assessing the efficacy results:

- For Study C-10-126,
  - **Step 1**: first test the treatment difference in the itching score between Olopatadine 0.77% and the Vehicle at the onset-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 2; otherwise no testing would be performed for the remaining hypothesis.
  - **Step 2**: test the treatment difference in the itching score between Olopatadine 0.77% and the Vehicle at 16-hour duration-of-action using a significant level of 5% (2-sided).

  (b) (4)

  the statistical reviewer also evaluated the efficacy results for the following two hypotheses sequentially:
  - For the treatment of ocular itching, Olopatadine 0.77% was superior to:
    - Vehicle at 24-hour duration-of-action;
    - PATADAY at 24-hour duration-of-action.

  For testing three time points within each hypothesis, the Bonferroni correction with a significance level of 0.017 for each time point was used.

- For Study C-12-053,
    - **Step 1**: first test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at the onset-of-action using a significant level of 5% (2-sided). If the test is statistically significant, proceed to Step 2; otherwise no testing would be performed for the remaining three hypotheses.
    - **Step 2**: test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at 24-hour duration-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 3; otherwise no testing would be performed for the remaining two hypotheses.
    - **Step 3**: test the treatment difference in the itching score between Olopatadine 0.77% and PATANOL at 24-hour duration-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 4; otherwise no testing would be performed for the remaining hypothesis.
    - **Step 4**: test the treatment difference in the itching score between Olopatadine 0.77% and PATADAY at 24-hour duration-of-action using a significant level of 5% (2-sided).
    - For testing three time points within each Step, the Bonferroni correction with a significance level of 0.017 for each time point was used.

It should be noted that the above approaches were conducted post-hoc and only served as a reference for the statistical reviewer to better understand the efficacy results. Comments recommending the gatekeeping approach were conveyed to the applicant at the protocol design stage; however, the applicant did not follow the recommendation.

In Study C-10-126, mixed model repeated measures (MMRM) analysis of variance was employed as the primary analysis method. The average of the scores from both eyes was the dependent variable in the model. The MMRM analysis included fixed effects terms for investigator, treatment (Olopatadine 0.77%, PATADAY or Vehicle), time, and treatment-by-time interaction. Investigator was included as a fixed effects term in the model so that the analysis model is consistent with the randomization scheme; randomization was stratified by Investigator site. An unstructured covariance matrix was used to model the within-patient errors. Furthermore, Kenward-Roger (KR) approximation was used to estimate denominator degrees of freedom. From the MMRM model, the least squares mean estimate of the treatment difference at each post-CAC time point between Olopatadine 0.77% vs. Vehicle were obtained.

In Study C-12-053, mixed model repeated measures (MMRM) analysis of variance was conducted as the primary analysis method. The score from each eye was the dependent variable in the model. The MMRM analysis included fixed effects terms for investigator, treatment (Olopatadine 0.77%, PATADAY, PATANOL or Vehicle), eye (right [OD] or left [OS]), time, and treatment-by-time interaction. Investigator was included as a fixed effects term in the model so that the analysis model is consistent with the randomization scheme – randomization was stratified by investigator site. An unstructured covariance matrix was used to model the within-patient errors. Furthermore, Kenward-Roger (KR) approximation was used to estimate denominator degrees of freedom. From the MMRM model, the least square mean estimate of the treatment difference at each post-CAC time point and the average treatment difference (over 3, 5

and 7 minutes post-CAC time points) between Olopatadine 0.77% vs. PATADAY, Olopatadine 0.77% vs. PATANOL and Olopatadine 0.77% vs. Vehicle were obtained.

The applicant primary analysis for Study C-12-053 used individual score from each eye (left or right) as the dependent variable, while the average of the scores from both eyes was the dependent variable in Study C-10-126. The applicant was aware of this difference during protocol design stage for Study C-12-053 and decided to use individual score. According to the applicant, the primary analysis approach used in C-12-053 was a more efficient approach since the analysis was based directly on the score as assessed for each eye and not on summaries; in addition, since the average was a sufficient statistic for the mean parameters of interest, the difference in approach was not expected to materially affect the estimates of within and between-treatment mean parameters. However, some information was expected to be lost by the summarization since the average was not a sufficient statistic for the variance parameters. The statistical reviewer considered both approaches acceptable; as expected, the efficacy results using both approaches were consistent.

The applicant also conducted additional analysis of the primary efficacy endpoint for Study C-10-126 using the same model as the one used in Study C-12-053 where dependent variable was individual score from each eye (left or right). Furthermore, additional analysis of the primary efficacy endpoint for Study C-12-053 was conducted by the statistical reviewer using the same model as the one used in Study C-10-126 where dependent variable was the average scores from both eyes for each subject.

The results of both approaches (average score from both eyes as dependent variable, or individual score from each eye as dependent variable) were similar for both studies. To simplify the presentation of the efficacy results for both studies and be consistent, the study results presented in this review were based on using the approach with individual score from each eye as dependent variable.

For the primary efficacy analysis, all data obtained were used in the analysis. Randomized patients who discontinue before efficacy visits (Visit 4A or 5 in Study C-10-126; Visit 3B and 4 in Study C-12-053) were excluded from the primary efficacy analyses. Among all 547 randomized subjects, two subjects from Study C-10-126 were excluded from the primary efficacy analyses due to discontinuation before efficacy visits; therefore the exclusion of subjects from the primary efficacy analyses had minimal impact on the final study results.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Two hundred and two patients were randomized into Study C-10-126, including 66 in the Olopatadine 0.77% group, 68 in the PATADAY (Olopatadine 0.2%) group, and 68 in the Vehicle group. Among these 202 subjects, sixteen patients discontinued the study early, and 186 (92.1%) completed the study. Among the 16 patients who discontinued early, slightly more patients (11.8% [8/68]) in the Vehicle group discontinued the study early compared to patients in the Olopatadine groups (4.5% [3/66], and 7.4% [5/68] for Olopatadine 0.77% group and PATADAY group respectively).

Three hundred and forty-five patients were randomized into Study C-12-053, including 98 in the Olopatadine 0.77% group, 99 in the PATADAY group, 99 in the PATANOL (Olopatadine 0.1%) group, and 49 in the Vehicle group. Among these 345 subjects, twenty patients discontinued the study early, and 325 (94.2%) completed the study. Among the 20 patients who discontinued early, less patients (2.0% [1/49]) in the Vehicle group discontinued the study early compared to patients in the Olopatadine groups (5.1% [5/99], 5.1% [5/99], and 9.1% [9/99] for Olopatadine 0.77% group, PATADAY group, and PATANOL group respectively).

Table 6: Subjects' Disposition for Studies C-10-126 and C-12-053

Study C-10-126					
	Olopatadine 0.77% n (%)	**PATADAY n (%)**	**PATANOL**	**Vehicle n (%)**	**Total N=202 n (%)**
Randomized	66 (100.0%)	68 (100.0%)	n/a	68 (100.0%)	202 (100.0%)
Treated	66 (100.0%)	68 (100.0%)	n/a	68 (100.0%)	202 (100.0%)
Completed	63 (95.5%)	63 (92.6%)	n/a	60 (88.2%)	186 (92.1%)
Discontinued	3 (4.5%)	5 (7.4%)	n/a	8 (11.8%)	16 (7.9%)
Adverse event	2 (3.0%)	0 (0.0%)	n/a	1 (1.5%)	3 (1.5%)
Lost to follow-up	1 (1.5%)	0 (0.0%)	n/a	2 (2.9%)	3 (1.5%)
Patient's decision	0 (0.0%)	0 (0.0%)	n/a	1 (1.5%)	1 (0.5%)
Other	0 (0.0%)	5 (7.4%)	n/a	4 (5.9%)	9 (4.5%)
Study C-12-053					
	Olopatadine 0.77% n (%)	**PATADAY n (%)**	**PATANOL**	**Vehicle n (%)**	**Total N=345 n (%)**
Randomized	98 (100.0%)	99 (100.0%)	99 (100.0%)	49 (100.0%)	345 (100.0%)
Treated	98 (100.0%)	99 (100.0%)	99 (100.0%)	49 (100.0%)	345 (100.0%)
Completed	93 (94.9%)	94 (94.9%)	90 (90.9%)	48 (98.0%)	325 (94.2%)
Discontinued	5 (5.1%)	5 (5.1%)	9 (9.1%)	1 (2.0%)	20 (5.8%)
Adverse event	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (0.6%)
Progressive Disease	1 (1.0%)	4 (4.0%)	3 (3.0%)	0 (0.0%)	8 (2.3%)
Protocol Violation	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	3 (0.9%)
Withdrawal by Patient	1 (1.0%)	0 (0.0%)	3 (3.0%)	1 (2.0%)	5 (1.4%)

Source: Table 10.1.-1 of Study C-10-126 report and Table 10.1.-1 of Study C-12-053 report.

For Study C-10-126 and Study C-12-053, no patients were excluded from the safety analysis. According to the protocol, randomized patients who discontinue before efficacy visits (Visit 4A or 5 in Study C-10-126) did not contributed to the efficacy analyses for that visit or subsequent visits, and therefore were excluded from the primary analysis dataset. The applicant excluded 2 patients from the ITT analyses because of patient discontinuation prior to a CAC; both patients were in the PATADAY group. For Study C-12-053, all patients were included in the ITT analysis.

Table 7: Analysis Population for Studies C-10-126 and C-12-053

Study C-10-126					
	Olopatadine 0.77% n (%)	**PATADAY n (%)**	**PATANOL**	**Vehicle n (%)**	**Total N=202 n (%)**
Safety Population	66 (100.0%)	68 (100.0%)	n/a	68 (100.0%)	202 (100.0%)
Intent-to-Treat (ITT)	66 (100.0%)	66 (97.1%)	n/a	68 (100.0%)	202 (100.0%)
Study C-12-053					
	Olopatadine 0.77% n (%)	**PATADAY n (%)**	**PATANOL**	**Vehicle n (%)**	**Total N=345 n (%)**
Safety Population	98 (100.0%)	99 (100.0%)	99 (100.0%)	49 (100.0%)	345 (100.0%)
Intent-to-Treat (ITT)	98 (100.0%)	99 (100.0%)	99 (100.0%)	49 (100.0%)	345 (100.0%)

Source: Table 10.1.-2 of Study C-10-126 report and Table 10.1.-1 of Study C-12-053 report.

As presented in the following tables, there were no noted differences in demographic and baseline characteristics among the treatment groups for all two studies.

Table 8: Study C-10-126 Demographic and Baseline Characteristics (ITT)

Characteristics	**Olopatadine 0.77% (N=66)**	**PATADAY n (%) (N=66)**	**Vehicle (N=68)**
	n (%)	**n (%)**	**n (%)**
Gender			
Male	23 (34.8%)	24 (36.4%)	29 (42.6%)
Female	43 (65.2%)	42 (63.6%)	39 (57.4%)
Age			
Mean (Std)	40.9 (13.1)	40.7 (14.2)	41.8 (13.3)
Min, Max	18, 68	18, 73	19, 77
18 to 64 Years	64 (97.0%)	64 (97.0%)	66 (97.1%)
≥ 65 Years	2 (3.0%)	2 (3.0%)	2 (2.9%)
Race			
White/Caucasian	50 (75.8%)	52 (78.8%)	57 (83.8%)
Black/African American	14 (21.2%)	11 (16.7%)	8 (11.8%)
Asian	1 (1.5%)	1 (1.5%)	1 (1.5%)
American Indian or Alaska	1 (1.5%)	1 (1.5%)	1 (1.5%)
Other	0 (0.0%)	1 (1.5%)	1 (1.5%)
Ethnicity			
Hispanic, Latino, or Spanish	7 (10.6%)	6 (9.1%)	4 (5.9%)
Not Hispanic, Latino, or Spanish	59 (89.4%)	60 (90.9%)	64 (94.1%)
Allergen Type			
Ragweed	23 (34.8%)	9 (13.6%)	18 (26.5%)
Grass	17 (25.8%)	22 (33.3%)	23 (33.8%)
Trees	7 (10.6%)	8 (12.1%)	5 (7.4%)
Dust Mites	11 (16.7%)	20 (30.3%)	11 (16.2%)
Cat Dander	7 (10.6%)	6 (9.1%)	10 (14.7%)
Dog Dander	1 (1.5%)	1 (1.5%)	1 (1.5%)

Characteristics	Olopatadine 0.77% (N=66) n (%)	PATADAY (N=66) n (%)	Vehicle (N=68) n (%)

Source: Tables 11.2.1.-1 and 11.2.1.-2 of Study C-10-126 report.

Table 9: Study C-12-053 Demographic and Baseline Characteristics (ITT)

Characteristics	Olopatadine 0.77% (N=98) n (%)	PATADAY (N=99) n (%)	PATANOL (N=99) n (%)	Vehicle (N=49) n (%)
Gender				
Male	37 (37.8%)	44 (44.4%)	43 (43.4%)	17 (34.7%)
Female	61 (62.2%)	55 (55.6%)	56 (56.6%)	32 (65.3%)
Age				
Mean (Std)	38.8 (12.7)	41.8 (13.7)	41.0 (12.2)	41.6 (12.3)
Min, Max	18, 66	18, 75	18, 72	18, 66
18 to 64 Years	97 (99.0%)	93 (93.9%)	95 (96.0%)	48 (98.0%)
≥ 65 Years	1 (1.0%)	6 (6.1%)	4 (4.0%)	1 (2.0%)
Race				
White/Caucasian	81 (82.7%)	70 (70.7%)	77 (77.8%)	35 (71.4%)
Black/African American	13 (13.3%)	26 (26.3%)	14 (14.1%)	9 (18.4%)
Asian	1 (1.0%)	1 (1.0%)	3 (3.0%)	2 (4.1%)
American Indian or Alaska	1 (1.0%)	0 (0.0%)	2 (2.0%)	2 (4.1%)
Multi-racial	1 (1.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)
Other	1 (1.0%)	2 (2.0%)	1 (1.0%)	1 (2.0%)
Ethnicity				
Hispanic, Latino, or Spanish	19 (19.4%)	14 (14.1%)	18 (18.2%)	8 (16.3%)
Not Hispanic, Latino, or Spanish	78 (79.6%)	85 (85.9%)	81 (81.8%)	41 (83.7%)
Allergen Type				
Ragweed	9 (9.2%)	7 (7.1%)	15 (15.2%)	9 (18.4%)
Grass	49 (50.0%)	51 (51.5%)	45 (45.5%)	22 (44.9%)
Trees	14 (14.3%)	16 (16.2%)	15 (15.2%)	9 (18.4%)
Dust Mites	13 (13.3%)	15 (15.2%)	17 (17.2%)	8 (16.3%)
Cat Dander	10 (10.2%)	5 (5.1%)	5 (5.1%)	3 (6.1%)
Dog Dander	1 (1.0%)	3 (3.0%)	1 (1.0%)	0 (0.0%)
Cockroach	2 (2.0%)	2 (2.0%)	1 (1.0%)	2 (4.1%)

Source: Tables 11.2.1.-1 of Study C-12-053 report.

3.2.4 Results and Conclusions

3.2.4.1 Ocular Itching

For both studies, the primary efficacy variable was patient-evaluated ocular itching severity scores. Scores were assessed using a 0-4 scale with 0.5 unit increments. Ocular itching was assessed for both eyes. In Study C-10-126, the applicant-defined primary efficacy endpoints

were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visits 4B (16-hour duration-of-action) and 5 (onset-of-action). In Study C-12-053, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at both Visit 3B (24-hour duration-of-action) and Visit 4 (onset-of-action).

The following inferences were based on the testing procedure proposed by the statistical reviewer in Section 3.2.2 Statistical Methodologies.

For Study C-10-126:

- At onset-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.54 (95% CI: [-1.82, -1.25]) at 3 minutes post-CAC; -1.53 (95% CI: [-1.84, -1.22]) at 5 minutes post-CAC; and -1.49 (95% CI: [-1.80, -1.18]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 16-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.50 (95% CI: [-1.77, -1.23]) at 3 minutes post-CAC; -1.48 (95% CI: [-1.79, -1.16]) at 5 minutes post-CAC; and -1.38 (95% CI: [-1.69, -1.07]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.61 (95% CI: [-1.88, -1.33]) at 3 minutes post-CAC; -1.51 (95% CI: [-1.81, -1.21]) at 5 minutes post-CAC; and -1.41 (95% CI: [-1.72, -1.11]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.48 (95% CI: [-0.76, -0.20]) at 3 minutes post-CAC; -0.42 (95% CI: [-0.72, -0.12]) at 5 minutes post-CAC; and -0.41 (95% CI: [-0.72, -0.10]) at 7 minutes post-CAC. The p-values at these three time points were all <0.01.

Study C-10-126 (b) (4) Olopatadine 0.77% compared with PATADAY for the treatment of ocular itching associated with allergic conjunctivitis at both onset-of-action and 16-hour duration-of-action.

- At onset-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.02 (95% CI: [-0.31, 0.26]) at 3 minutes post-CAC; -0.08 (95% CI: [-0.39, 0.22]) at 5 minutes post-CAC; and -0.13 (95% CI: [-0.44, 0.17]) at 7 minutes post-CAC.
- At 16-hour duration-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.17 (95% CI: [-0.44, 0.11]) at 3 minutes post-CAC; -0.24 (95% CI: [-0.55, 0.07]) at 5 minutes post-CAC; and -0.23 (95% CI: [-0.54, -0.08]) at 7 minutes post-CAC.

For Study C-12-053:

- At onset-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.53 (95% CI: [-1.76, -1.30]) at 3 minutes post-CAC; -1.46 (95% CI: [-1.71, -1.22]) at 5 minutes post-CAC; and -1.17 (95% CI: [-1.45, -0.90]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.29 (95% CI: [-1.60, -0.97]) at 3 minutes post-CAC; -1.15 (95% CI: [-1.46, -0.84]) at 5 minutes post-CAC; and -0.89 (95% CI: [-1.22, -0.57]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATANOL dosed once a day (instead of the approved twice-daily regimen) for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and PATANOL were -0.52 (95% CI: [-0.78, -0.27]) at 3 minutes post-CAC; -0.48 (95% CI: [-0.73, -0.23]) at 5 minutes post-CAC; and -0.39 (95% CI: [-0.65, -0.12]) at 7 minutes post-CAC. The p-values at these three time points were all <0.01.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis at 3 and 5 minutes (b) (4) post-CAC. The point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.31 (95% CI: [-0.57, -0.06]; p-value=0.0156) at 3 minutes post-CAC; -0.26 (95% CI: [-0.51, -0.01]; p-value=0.046) at 5 minutes post-CAC; and -0.16 (95% CI: [-0.42, 0.11]; p-value=0.25) at 7 minutes post-CAC.

Study C-12-053 (b) (4) Olopatadine 0.77% compared with PATADAY for the treatment of ocular itching associated with allergic conjunctivitis at onset-of-action.

- At onset-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.09 (95% CI: [-0.28, 0.09]) at 3 minutes post-CAC; -0.08 (95% CI: [-0.29, 0.12]) at 5 minutes post-CAC; and 0.04 (95% CI: [-0.18, 0.26]) at 7 minutes post-CAC.

Table 10: Study C-10-126 Analysis of Ocular Itching Score* (ITT)

	Onset-of-Action			16-Hour Duration-of-Action			24-Hour Duration-of-Action		
	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)
3 Minutes	0.36	0.39	1.90	0.70	0.87	2.20	0.93	1.41	2.54
Difference		-0.02	-1.54		-0.17	-1.50		-0.48	-1.61
(95% CI)		(-0.31, 0.26)	(-1.82, -1.25)		(-0.44, 0.11)	(-1.77, -1.23)		(-0.76, -0.20)	(-1.88, -1 33)
5 Minutes	0.53	0.61	2.06	0.79	1.04	2.27	1.10	1.52	2.62
Difference		-0.08	-1.53		-0.24	-1.48		-0.42	-1.51
(95% CI)		(-0.39, 0.22)	(-1.84, -1.22)		(-0.55, 0.07)	(-1.79, -1.16)		(-0.72, -0.12)	(-1.81, -1 21)
7 Minutes	0.48	0.61	1.97	0.75	0.98	2.13	1.09	1.50	2.50
Difference		-0.13	-1.49		-0.23	-1.38		-0.41	-1.41
(95% CI)		(-0.44, 0.17)	(-1.80, -1.18)		(-0.54, 0.08)	(-1.69, -1.07)		(-0.72, -0.10)	(-1.72, -1 11)

Average	0.46	0.54	1.98	0.75	0.96	2.20	1.04	1.48	2.55
Difference		-0.08	-1.51		-0.21	-1.45		-0.44	-1.51
(95% CI)		(-0.37, 0.21)	(-1.81, -1.23)		(-0.49, 0.07)	(-1.73, -1.17)		(-0.72, -0.16)	(-1.79, -1 24)

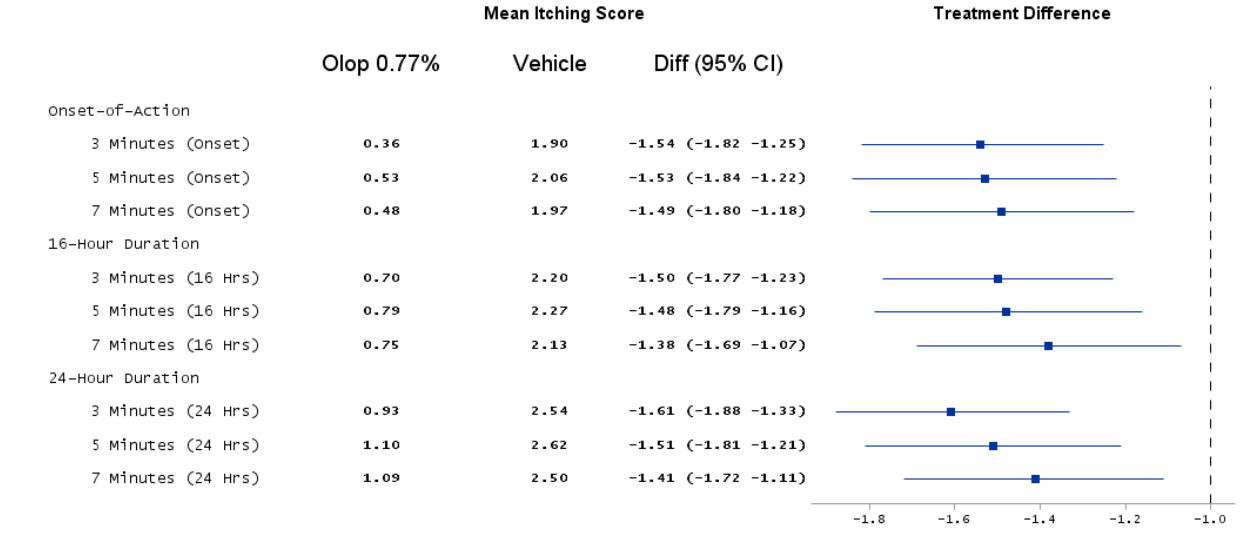
* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.
Source: Tables 2.7.3.2-2, 2.7.3.2-3, and 2.7.3.2-7 of Summary of Clinical Efficacy.

Table 11: Study C-12-053 Analysis of Ocular Itching Score* (ITT)

	Onset-of-Action				24-Hour Duration-of-Action			
	Olopatadine 0.77% (N=98)	**PATADAY[1] (N=99)**	**PATANOL (N=99)**	**Vehicle (N=49)**	**Olopatadine 0.77% (N=98)**	**PATADAY (N=99)**	**PATANOL[1] (N=99)**	**Vehicle (N=49)**
3 Minutes	0.38	0.47	0.59	1.91	1.01	1.33	1.53	2.30
Difference		-0.09	-0.21	-1.53		-0.31	-0.52	-1.29
(95% CI)		(-0.28, 0.09)	(-0.40, -0.02)	(-1.76, -1.30)		(-0.57, -0.06)	(-0.78, -0.27)	(-1.60, -0.97)
5 Minutes	0.53	0.61	0.79	1.99	1.22	1.48	1.70	2.37
Difference		-0.08	-0.26	-1.46		-0.26	-0.48	-1.15
(95% CI)		(-0.29, 0.12)	(-0.47, -0.06)	(-1.71, -1.22)		(-0.51, -0.01)	(-0.73, -0.23)	(-1.46, -0.84)
7 Minutes	0.65	0.61	0.83	1.82	1.25	1.41	1.64	2.14
Difference		0.04	-0.18	-1.17		-0.16	-0.39	-0.89
(95% CI)		(-0.18, 0.26)	(-0.41, 0.04)	(-1.45, -0.90)		(-0.42, 0.11)	(-0.65, -0.12)	(-1.22, -0.57)
Average	0.52	0.56	0.74	1.91	1.16	1.40	1.62	2.27
Difference		-0.05	-0.22	-1.39		-0.24	-0.46	-1.11
(95% CI)		(-0.24, 0.14)	(-0.41, -0.03)	(-1.62, -1.16)		(-0.48, -0.00)	(-0.70, -0.23)	(-1.40, -0.82)

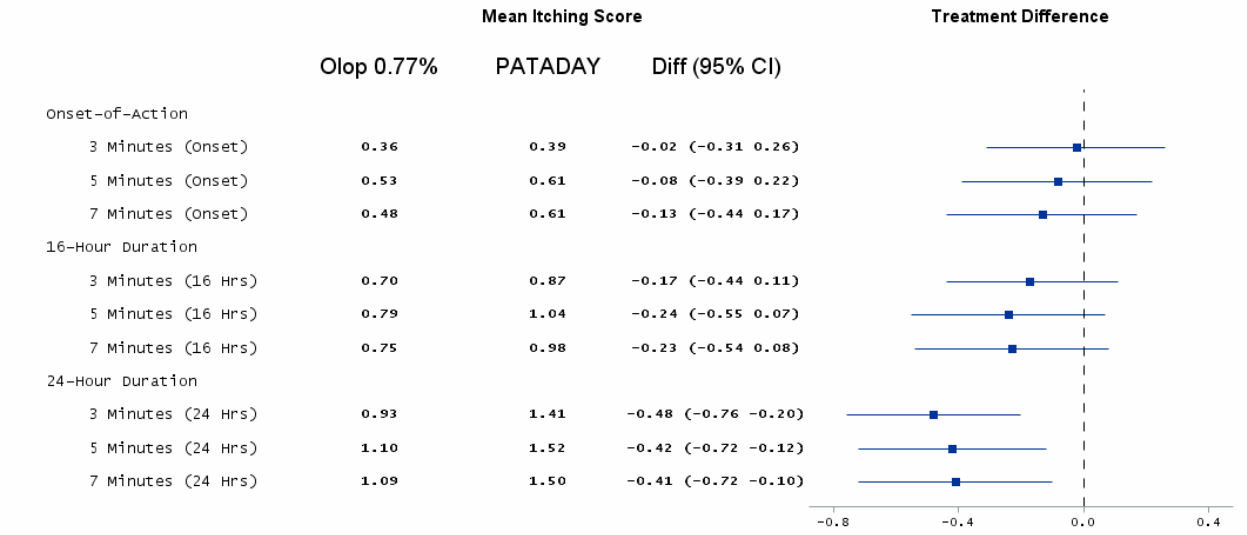
* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.
[1] PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action).
Source: Tables 2.7.3.2-10, and 2.7.3.2-11 of Summary of Clinical Efficacy.

Figure 1: Study C-10-126 Analysis of Ocular Itching Score* (Olopatadine 0.77% vs. Vehicle, ITT)



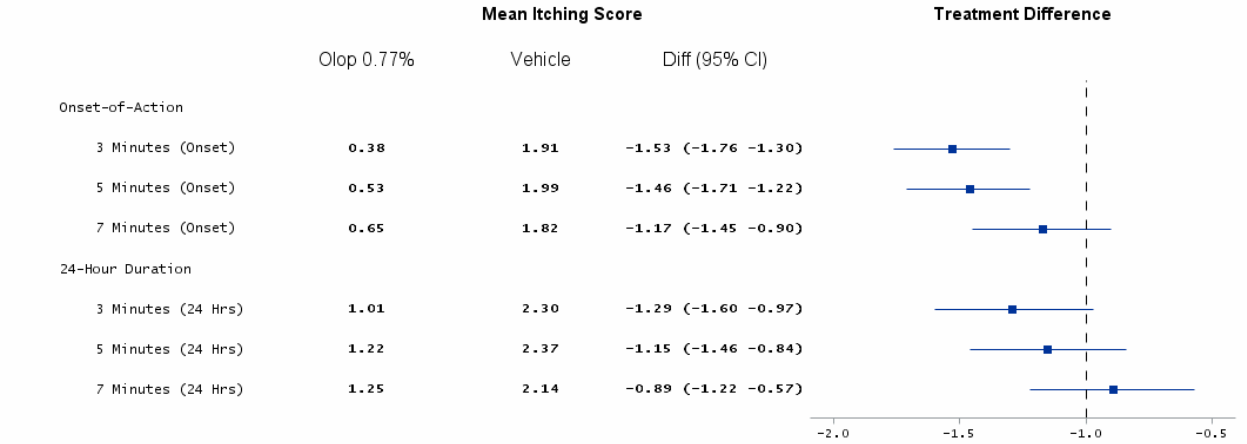
* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction
Source: Tables 2 7 3 2-2, 2 7 3 2-3, and 2 7 3 2-7 of Summary of Clinical Efficacy

Figure 2: Study C-10-126 Analysis of Ocular Itching Score* (Olopatadine 0.77% vs. PATADAY, ITT)



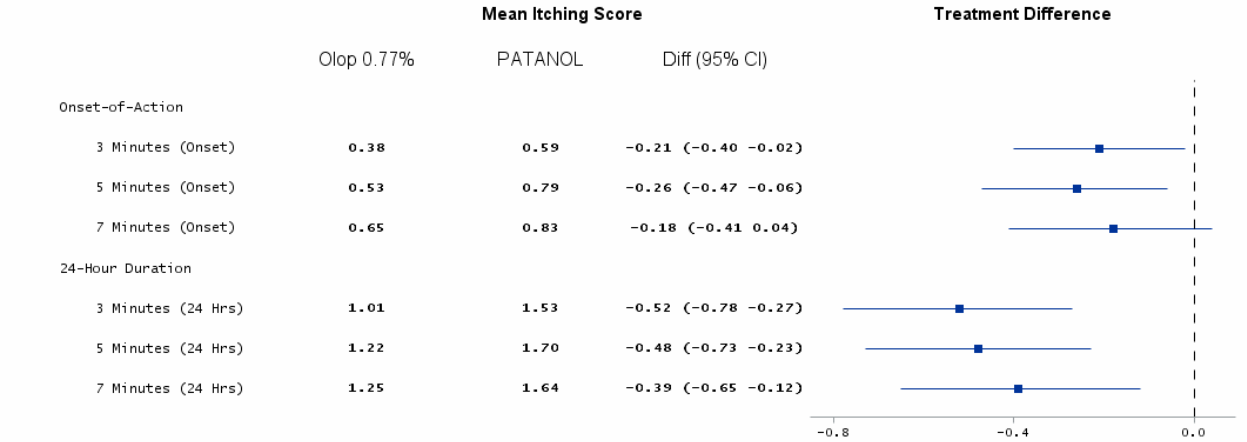
* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction
Source: Tables 2 7 3 2-2, 2 7 3 2-3, and 2 7 3 2-7 of Summary of Clinical Efficacy

Figure 3: Study C-12-053 Analysis of Ocular Itching Score* (Olopatadine 0.77% vs. Vehicle, ITT)



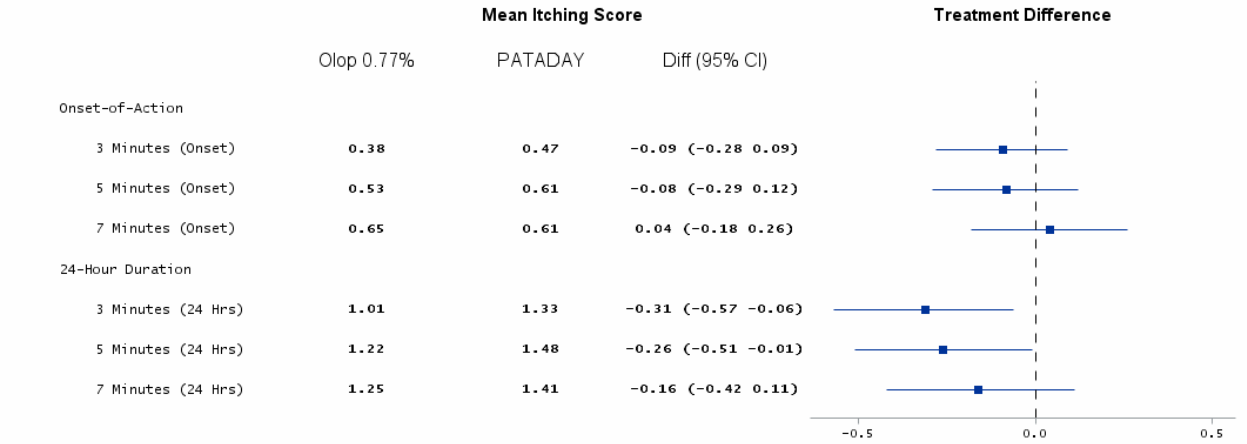
* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction
Source: Tables 2 7 3 2-10, and 2 7 3 2-11 of Summary of Clinical Efficacy

Figure 4: Study C-12-053 Analysis of Ocular Itching Score* (Olopatadine 0.77% vs. PATANOL, ITT)



* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction
PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action)
Source: Tables 2 7 3 2-10, and 2 7 3 2-11 of Summary of Clinical Efficacy

Figure 5: Study C-12-053 Analysis of Ocular Itching Score* (Olopatadine 0.77% vs. PATADAY, ITT)



* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction
Source: Tables 2 7 3 2-10, and 2 7 3 2-11 of Summary of Clinical Efficacy

Additional sensitivity analyses for ocular itching (based on observed data) without modeling were conducted by the statistical reviewer. The statistical reviewer calculated descriptive statistics for ocular itching at onset-of-action and at 16-hour duration-of-action of Study C-10-126 and for ocular itching at onset-of-action and at 24-hour duration-of-action of Study C-12-053 were listed in the following two tables. The tables also included the treatment differences between treatment groups and their corresponding 95% confidence intervals (CIs); the differences were the point estimates of the mean differences without any modeling and the 95% CIs were calculated based on normal approximation to continuous data. These results were consistent with the primary analysis results.

Table 12: Descriptive Statistics for Ocular Itching for Studies C-10-126 (ITT Observed)

	Onset-of-Action (Visit 5)					
	Mean (STD)			Difference (95% CI)[a]		
Min	Olopatadine 0.77% (N=63)	PATADAY (N=63)	Vehicle (N=60)	Olopatadine 0.77% Vs. Vehicle	PATADAY vs. Vehicle	Olopatadine 0.77% Vs. PATADAY
3	0.42 (0.69)	0.44 (0.55)	1.93 (1.09)	-1.52 (-1.84, -1.19)	-1.49 (-1.81, -1.18)	-0.02 (-0.24, 0.20)
5	0.58 (0.76)	0.67 (0.72)	2.09 (1.08)	-1.51 (-1.85, -1.18)	-1.42 (-1.75, -1.09)	-0.09 (-0.35, 0.17)
7	0.53 (0.71)	0.67 (0.79)	2.01 (1.06)	-1.48 (-1.80, -1.15)	-1.34 (-1.68, -1.01)	-0.13 (-0.40, 0.13)
	16-Hour Duration-of-Action (Visit 4B)					
	Mean (STD)			Difference (95% CI)[a]		
Min	Olopatadine 0.77% (N=65)	PATADAY (N=65)	Vehicle (N=65)	Olopatadine 0.77% Vs. Vehicle	PATADAY vs. Vehicle	Olopatadine 0.77% Vs. PATADAY
3	0.71 (0.93)	0.9 (0.76)	2.21 (0.88)	-1.50 (-1.78, -1.22)	-1.31 (-1.59, -1.02)	-0.19 (-0.45, 0.06)
5	0.79 (0.82)	1.07 (0.96)	2.26 (0.92)	-1.47 (-1.77, -1.17)	-1.19 (-1.52, -0.87)	-0.28 (-0.59, 0.03)
7	0.88 (1.32)	1.02 (0.91)	2.13 (0.95)	-1.38 (-1.69, -1.06)	-1.11 (-1.44, -0.79)	-0.26 (-0.57, 0.04)
	24-Hour Duration-of-Action (Visit 3B)					
	Mean (STD)			Difference (95% CI)[a]		
Min	Olopatadine 0.77% (N=66)	PATADAY (N=66)	Vehicle (N=68)	Olopatadine 0.77% Vs. Vehicle	PATADAY vs. Vehicle	Olopatadine 0.77% Vs. PATADAY
3	0.91 (0.81)	1.39 (0.84)	2.50 (0.76)	-1.58 (-1.85, -1.31)	-1.11 (-1.39, -0.83)	-0.47 (-0.76, -0.19)
5	1.09 (0.88)	1.49 (0.91)	2.57 (0.84)	-1.48 (-1.77, -1.19)	-1.08 (-1.38, -0.78)	-0.39 (-0.70, -0.09)
7	1.08 (0.86)	1.46 (0.97)	2.46 (0.85)	-1.38 (-1.67, -1.08)	-0.99 (-1.31, -0.68)	-0.38 (-0.70, -0.07)

[a] 95% CI calculated based on normal approximation to continuous data.
Source: Statistical Reviewer's calculation.

Table 13: Descriptive Statistics for Ocular Itching for Studies C-12-053 (ITT Observed)

	Onset-of-action[1] (Visit 5)								
	Mean (STD)				Difference (95% CI)[a]				
MIN	Olop 0.77% (N=93)	PATADAY (N=94)	PATANOL (N=90)	Vehicle (N=48)	Olop 0.77% Vs. Vehicle	PATADAY vs. Vehicle	PATANOL Vs. Vehicle	Olop 0.77% Vs. PATADAY	Olop 0.77% Vs. PATANOL
3	0.42 (0.50)	0.52 (0.54)	0.62 (0.66)	1.93 (0.99)	-1.51 (-1.81, -1.20)	-1.40 (-1.71, -1.10)	-1.30 (-1.62, -0.98)	-0.10 (-0.25, 0.05)	-0.21 (-0.38, -0.04)
5	0.56 (0.62)	0.66 (0.59)	0.83 (0.74)	2.00 (0.95)	-1.43 (-1.73, -1.13)	-1.33 (-1.63, -1.03)	-1.17 (-1.48, -0.86)	-0.10 (-0.27, 0.07)	-0.26 (-0.46, -0.06)
7	0.69 (0.72)	0.67 (0.63)	0.87 (0.90)	1.81 (0.95)	-1.12 (-1.43, -0.81)	-1.14 (-1.40, -0.87)	-0.94 (-1.26, -0.61)	0.02 (-0.17, 0.22)	-0.18 (-0.41, 0.05)
	24-Hour Duration-of-Action[1] (Visit 3B)								
	Mean (STD)				Difference (95% CI)[a]				
MIN	Olop 0.77% (N=96)	PATADAY (N=99)	PATANOL (N=99)	Vehicle (N=48)	Olopatadine 0.77% Vs. Vehicle	PATADAY vs. Vehicle	PATANOL Vs. Vehicle	Olopatadine 0.77% Vs. PATADAY	Olopatadine 0.77% Vs. PATANOL
3	0.97 (0.85)	1.28 (0.93)	1.50 (0.92)	2.23 (0.97)	-1.26 (-1.57, -0.95)	-0.95 (-1.29, -0.63)	-0.73 (-1.06, -0.40)	-0.31 (-0.56, -0.06)	-0.53 (-0.78, -0.28)
5	1.19 (0.94)	1.42 (0.96)	1.67 (0.90)	2.33 (0.82)	-1.14 (-1.45, -0.82)	-0.90 (-1.22, -0.58)	-0.66 (-0.96, -0.35)	-0.23 (-0.50, 0.03)	-0.48 (-0.74, -0.22)
7	1.21 (0.99)	1.35 (0.96)	1.61 (1.00)	2.09 (0.84)	-0.88 (-1.21, -0.55)	-0.75 (-1.07, -0.43)	-0.48 (-0.81, -0.15)	-0.13 (-0.41, 0.14)	-0.40 (-0.68, -0.12)

[a] 95% CI calculated based on normal approximation to continuous data.
[1] PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action).
Source: Statistical Reviewer's calculation.

Additional supportive sensitivity analyses conducted by the applicant based on observed data only, based on PP analysis sets were also supportive of the primary efficacy results.

The approved regimen for PATANOL was twice daily; however, in Study C-12-053 that comparing Olopatadine 0.77% with PATANOL at 24-hour duration-of-action, PATANOL was dosed for only once (instead of the approved twice-a-day regimen) in the previous day. (b) (4)

In conclusion:

- In both studies, Olopatadine 0.77% was superior to Vehicle for treating ocular itching associated with allergic conjunctivitis at onset-of-action, and 24-hour duration-of-action.
- In Study C-10-126, at 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. In Study C-12-053, Olopatadine 0.77% was superior to PATADAY for ocular itching associated with allergic conjunctivitis at 24-hour duration-of-action at 2 (3 and 5 minutes) out of 3 post CAC time points. The point estimate for the treatment difference at 7 minutes post-CAC was in favor of Olopatadine 0.77% but did not demonstrate statistical significance.

Although in Study C-12-053, (b) (4) he study results were consistent between Study C-12-053 and Study C-10-126 and all in favor of Olopatadine 0.77%. In addition, in both studies, comparing with Vehicle, the ocular itching treatment effects of Olopatadine 0.77% were highly significant (p-value<0.0001) at all three time points in all the study visits. Therefore, this reviewer concluded that there is enough evidence to support the efficacy of Olopatadine 0.77% for the treatment of ocular itching associated with allergic conjunctivitis.

(b) (4)

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(b) (4)

(b) (4)

3.3 Evaluation of Safety

For Study C-10-126, all 202 subjects who were exposed to the study treatment were included in the safety analysis set. For Study C-12-053, all 345 subjects who were exposed to the study treatment were included in the safety analysis set. The following tables present the treatment-emergent adverse events for both studies.

Table 18: Summary of Treatment-Emergent Adverse Events of Studies C-10-126 (Safety Analysis Set)

	Olopatadine 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)
Patients discontinued due to an adverse event	**2 (3.0%)**	**0 (0.0%)**	**1 (1.5%)**
Discontinued due to non-fatal serious adverse events	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinued due to non-serious adverse events	2 (3.0%)	0 (0.0%)	1 (1.5%)
Treatment-related	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not related to treatment	2 (3.0%)	0 (0.0%)	1 (1.5%)
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	**6 (9.1%)**	**5 (7.4%)**	**5 (7.4%)**
Most frequent treatment-emergent adverse events (reported by 1% or more of the patients in either Treatment group)			
Conjunctival hemorrhage	1 (1.5%)	0 (0.0%)	0 (0.0%)
Punctate keratitis	0 (0.0%)	1 (1.5%)	0 (0.0%)
Vision blurred	0 (0.0%)	0 (0.0%)	1 (1.5%)
Gastroenteritis viral	2 (3.0%)	0 (0.0%)	0 (0.0%)
Diverticulitis	1 (1.5%)	0 (0.0%)	0 (0.0%)
Ear infection	0 (0.0%)	0 (0.0%)	1 (1.5%)
Influenza	0 (0.0%)	0 (0.0%)	1 (1.5%)
Nasopharyngitis	0 (0.0%)	0 (0.0%)	1 (1.5%)
Rhinitis	0 (0.0%)	0 (0.0%)	1 (1.5%)
Injury	1 (1.5%)	0 (0.0%)	1 (1.5%)
Arthralgia	1 (1.5%)	1 (1.5%)	0 (0.0%)
Headache	1 (1.5%)	1 (1.5%)	0 (0.0%)
Cough	0 (0.0%)	0 (0.0%)	1 (1.5%)
Urticaria	0 (0.0%)	1 (1.5%)	0 (0.0%)
Patients with at least 1 treatment-emergent adverse event	**1 (1.5%)**	**0 (0.0%)**	**1 (1.5%)**

related to treatment (ADR; adverse drug reaction)			
Vision blurred	0 (0.0%)	0 (0.0%)	1 (1.5%)
Headache	1 (1.5%)	1 (1.5%)	0 (0.0%)

Source: Table 12.2.2-1 of Study C-10-126 report.

Table 19: Summary of Treatment-Emergent Adverse Events of Studies C-12-053 (Safety Analysis Set)

	Olopatadine 0.77% (N=98)	**PATADAY (N=99)**	**PATANOL (N=99)**	**Vehicle (N=49)**
Patients discontinued due to an adverse event	**2 (2.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Discontinued due to non-fatal serious adverse events	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinued due to non-serious adverse events	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment-related	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not related to treatment	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	**10 (10.2%)**	**2 (2.0%)**	**7 (7.1%)**	**3 (6.1%)**
Most frequent treatment-emergent adverse events (reported by 1% or more of the patients in either Treatment group)				
Eye irritation	2 (2.0%)	0 (0.0%)	1 (1.0%)	1 (2.0%)
Vision blurred	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (2.0%)
Visual acuity reduced	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Conjunctival hemorrhage	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Lacrimation increased	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Gastroenteritis viral	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Influenza	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oral herpes	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Pharyngitis streptococcal	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Laceration	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Procedural pain	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Intraocular pressure increased	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Dysgeusia	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Migraine	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Cough	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Oropharyngeal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Patients with at least 1 treatment-emergent adverse event related to treatment (ADR; adverse drug reaction)	**2 (2.0%)**	**0 (0.0%)**	**1 (1.0%)**	**1 (2.0%)**
Eye irritation	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (2.0%)
Vision blurred	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Dysgeusia	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Table 12.2.2.-1 of Study C-12-053 report.

In addition, the applicant also conducted a long-term safety study C-10-128 during which, approximately 500 eligible subjects 2 years of age and older were randomized at 2:1 ratio to be dosed with one drop of Olopatadine 0.77% or Vehicle once daily in both eyes for 6 consecutive weeks. The majority of common adverse events (occurring at an incidence of ≥ 1%) reported in the Olopatadine 0.77% group during the safety study (C-12-028) were local ocular side effects and were also reported in the Vehicle group at similar incidences. Dysgeusia (a distortion of the sense of taste) was the single unique common adverse event reported in the Olopatadine 0.77%. Dysgeusia, which, according to the applicant, is typically due to the presence of active study drug, is not an uncommon occurrence after instillation of eye drops.

Table 20: Summary of Treatment-Emergent Adverse Events of Studies C-10-128 (Safety Analysis Set)

	Olopatadine 0.77% (N=330)	Vehicle (N=169)
Patients discontinued due to an adverse event	**0 (0.0%)**	**2 (1.2%)**
Discontinued due to non-fatal serious adverse events	0 (0.0%)	0 (0.0%)
Discontinued due to non-serious adverse events	0 (0.0%)	2 (1.2%)
Treatment-related	0 (0.0%)	0 (0.0%)
Not related to treatment	0 (0.0%)	2 (1.2%)
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	**88 (26.7%)**	**53 (31.4%)**
Most frequent treatment-emergent adverse events (reported by 1% or more of the patients in either Treatment group)		
Vision blurred	16 (4.8%)	7 (4.1%)
Dry eye	11 (3.3%)	5 (3.0%)
Abnormal sensation in eye	7 (2.1%)	7 (4.1%)
Eye pruritus	5 (1.5%)	2 (1.2%)
Eye irritation	1 (0.3%)	5 (3.0%)
Conjunctival hemorrhage	0 (0.0%)	2 (1.2%)
Diarrhea	0 (0.0%)	2 (1.2%)
Nasopharyngitis	6 (1.8%)	3 (1.8%)
Upper respiratory tract infection	6 (1.8%)	3 (1.8%)
Gastroenteritis viral	0 (0.0%)	2 (1.2%)
Ligament sprain	1 (0.3%)	2 (1.2%)
Corneal staining	8 (2.4%)	7 (4.1%)
Conjunctival staining	6 (1.8%)	1 (0.6%)
Dysgeusia	8 (2.4%)	0 (0.0%)
Headache	1 (0.3%)	2 (1.2%)
Cough		
Patients with at least 1 treatment-emergent adverse event related to treatment (ADR; adverse drug reaction)	**53 (16.1%)**	**31 (18.3%)**
Vision blurred	15 (4.5%)	7 (4.1%)
Abnormal sensation in eye	7 (2.1%)	7 (4.1%)
Dry eye	8 (2.4%)	5 (3.0%)
Eye irritation	1 (0.3%)	5 (3.0%)
Corneal staining	8 (2.4%)	7 (4.1%)
Conjunctival staining	6 (1.8%)	1 (0.6%)
Dysgeusia	8 (2.4%)	0 (0.0%)

Source: Table 12.2.2.-1 of Study C-10-128 report.

Please see the review of the medical reviewer for details of the safety evaluation.

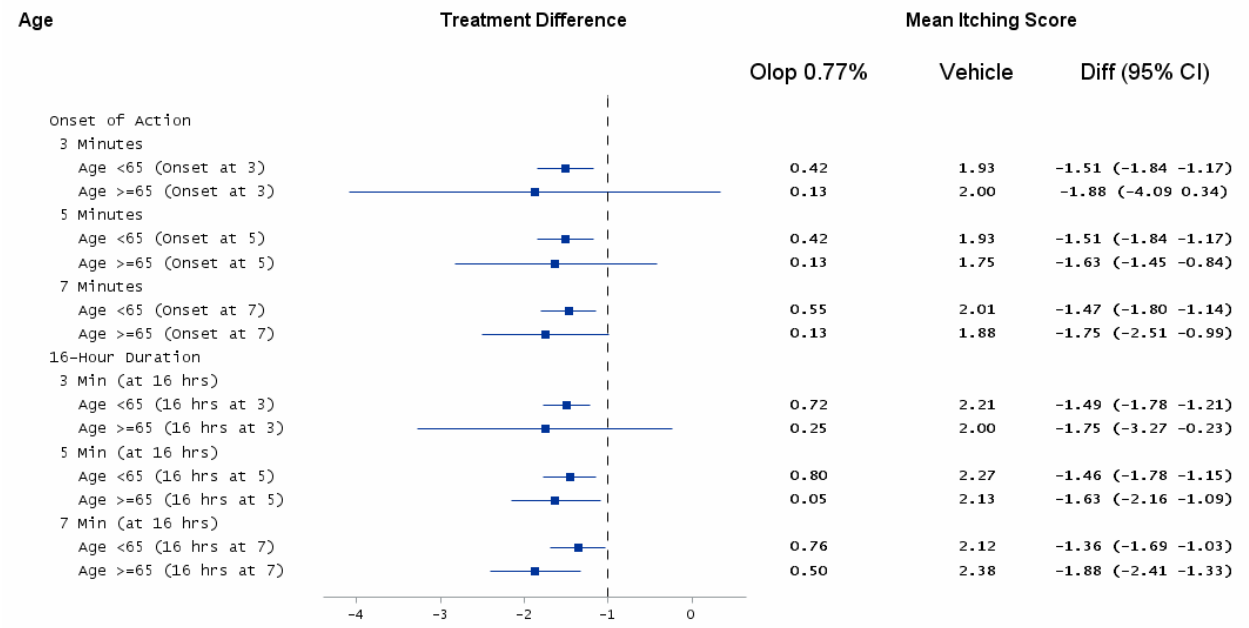
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

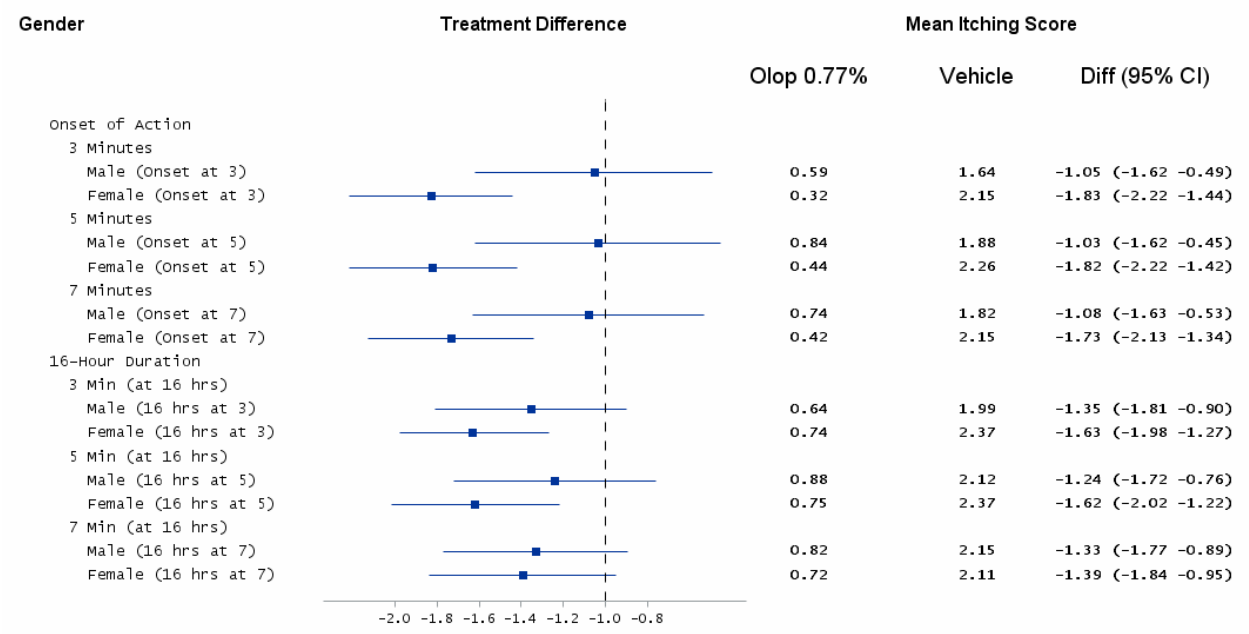
4.1 Age, Gender, and Race

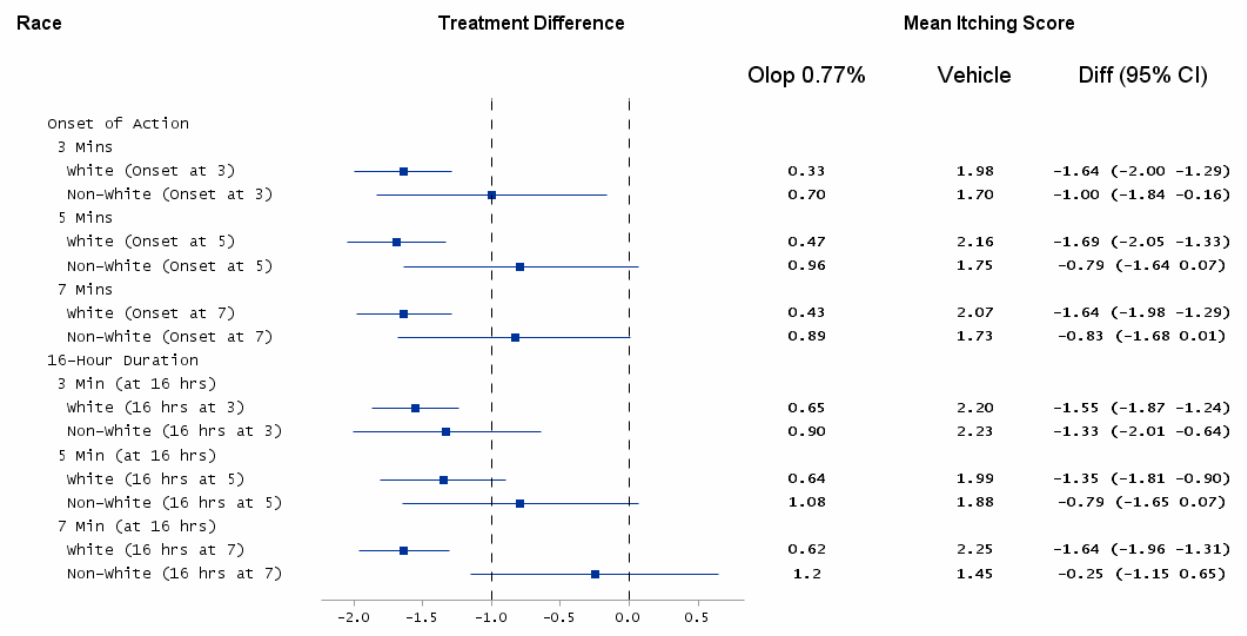
Subgroup analyses based on gender, race, and age for both studies were performed.

For both Study C-10-126 and Study C-12-053, in general, there were no marked differences in the efficacy results among the various subpopulations.

Figure 6: Forest Plots of Subgroup Analyses for Studies C-10-126 (Olopatadine 0.77% vs. Vehicle at Onset-of-action and 16-hour Duration)

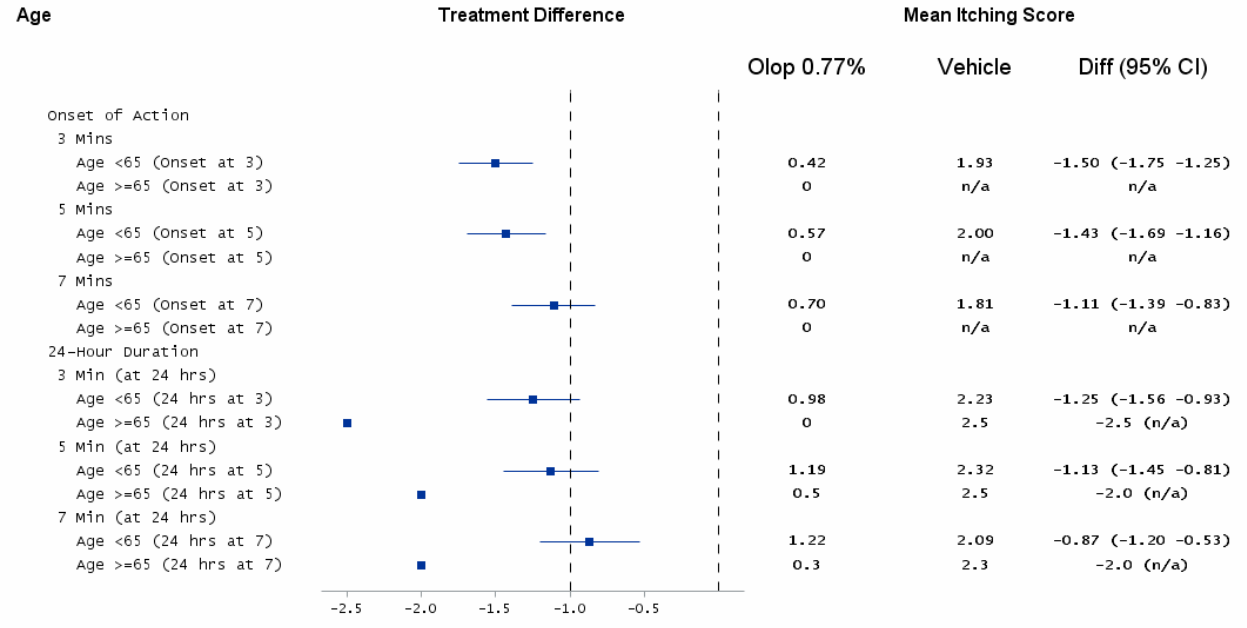


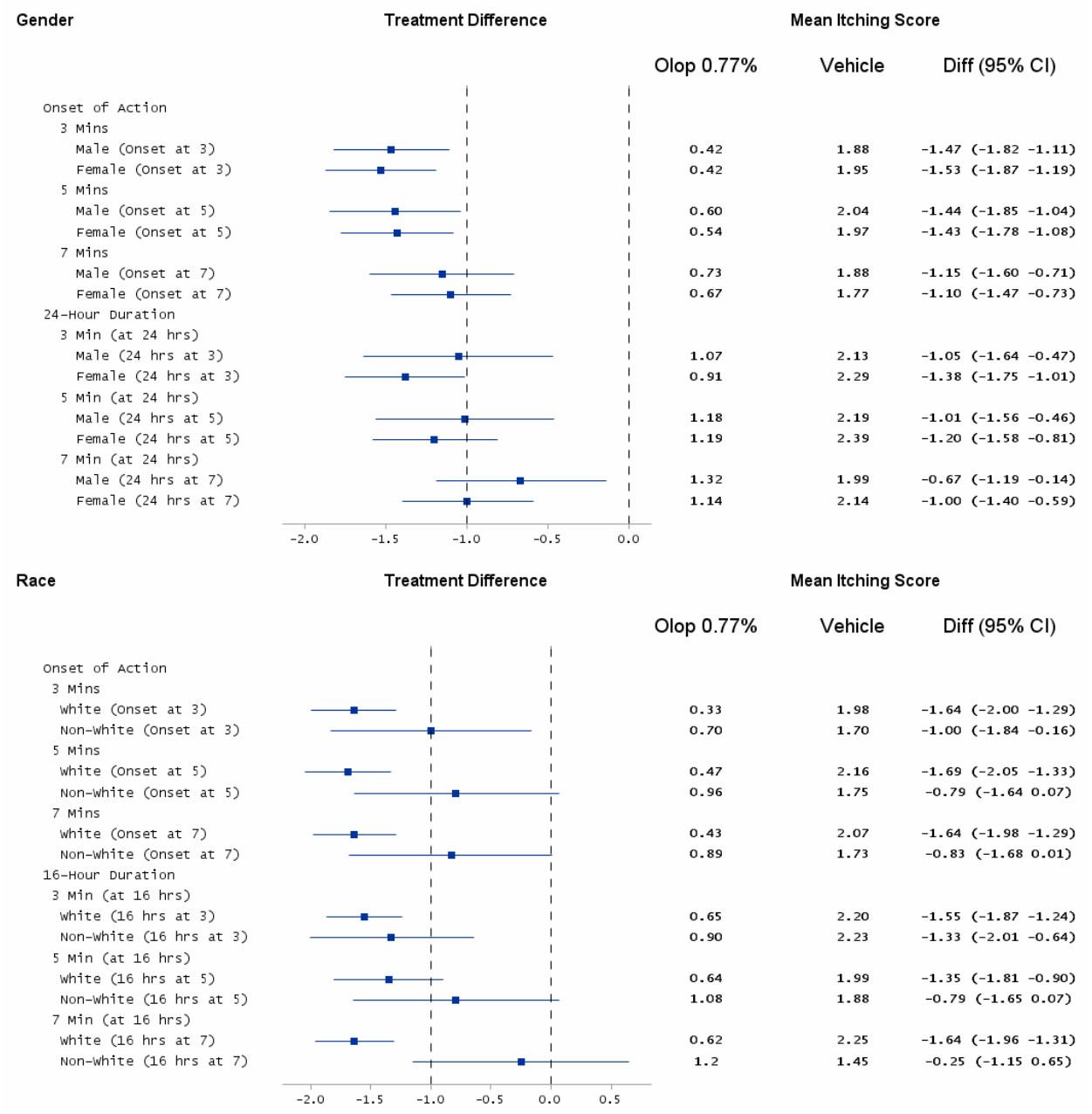




95% CI calculated based on normal approximation to continuous data.
Source: Statistical reviewer's analyses.

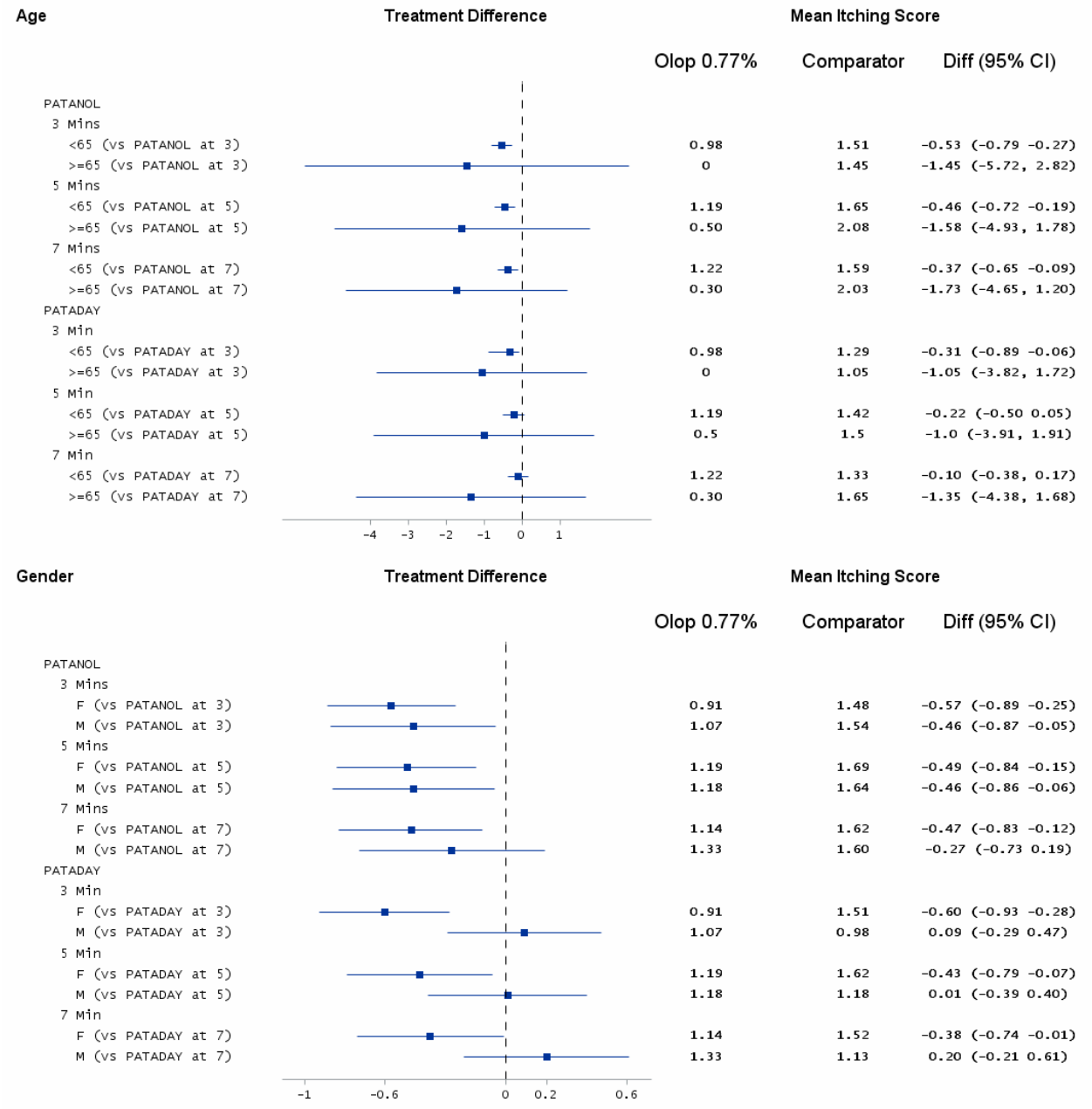
Figure 7: Forest Plots of Subgroup Analyses for Studies C-12-053 (Olopatadine 0.77% vs. Vehicle at Onset-of-action and 24-hour Duration)

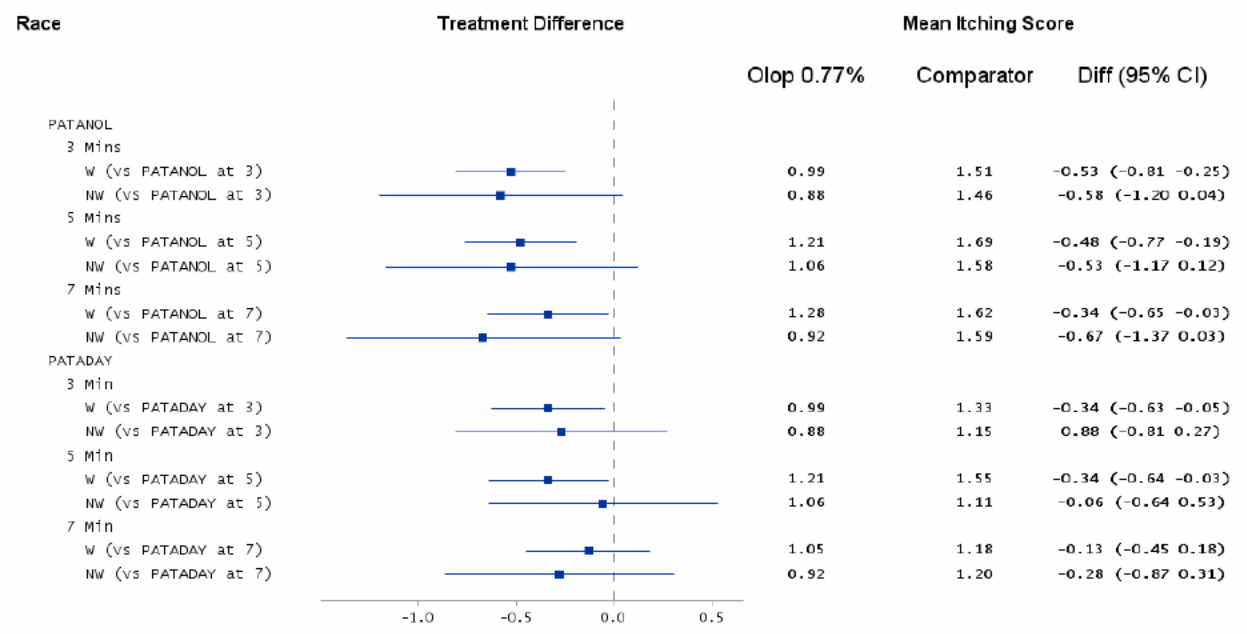




95% CI calculated based on normal approximation to continuous data.
Source: Statistical reviewer's analyses.

Figure 8: Forest Plots of Subgroup Analyses for Studies C-12-053 (Olopatadine 0.77% vs. PANANOL and Olopatadine 0.77% vs. PANADAY at 24-hour Duration)





95% CI calculated based on normal approximation to continuous data.
Source: Statistical reviewer's analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the two pivotal studies reviewed.

The primary efficacy hypotheses for Study C-10-126 were Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at:

- Onset-of-action
- 16-hour duration-of-action

(b) (4)

the statistical reviewer also examined the efficacy results for the following two hypotheses in Study C-10-126:

- For the treatment of ocular itching, Olopatadine 0.77% was superior to:
    - Vehicle at 24-hour duration-of-action;
    - PATADAY at 24-hour duration-of-action.

The primary efficacy hypotheses for Study C-12-053 were for the treatment of ocular itching, Olopatadine 0.77% was superior to:

- Vehicle at the onset-of-action;
- Vehicle at 24-hour duration-of-action;

(b) (4)

- PATADAY at 24-hour duration-of-action.

In both studies, the applicant defined all the primary efficacy hypotheses as co-primary hypotheses, which meant that the success criterion for each study was that all co-primary hypotheses must be statistically significant at the 5% level; otherwise, the study would be considered as failure. During the protocol design stage of Study C-12-053, the statistical reviewer reminded the applicant that for Study C-12-053 the success criterion of rejecting four hypotheses simultaneously might be hard to achieve; the statistical reviewer also suggested gatekeeping testing approach that rejected the four hypotheses sequentially as an alternative. However, the applicant still proceeded with the success criterion for Study C-12-053 being that all four primary hypotheses must be rejected at the 5% level simultaneously.

For both studies, at each study visit (onset-of-action and 16/24-hour duration-of-action), the applicant stated that statistical significance was required at 2 out of 3 time points to demonstrate superiority of Olopatadine 0.77% over Vehicle (b) (4) or PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. However, this approach would not control the overall Type I error rate since there were three different scenarios (b) (4)

In order to better understand the study results with the overall Type I error for each study being controlled, the statistical reviewer considered the following approach while assessing the efficacy results:

- For Study C-10-126,
  - **Step 1**: first test the treatment difference in the itching score between Olopatadine 0.77% and the Vehicle at the onset-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 2; otherwise no testing would be performed for the remaining hypothesis.
  - **Step 2**: test the treatment difference in the itching score between Olopatadine 0.77% and the Vehicle at 16-hour duration-of-action using a significant level of 5% (2-sided).

(b) (4)

the statistical reviewer also evaluated the efficacy results for the following two hypotheses sequentially:

  - For the treatment of ocular itching, Olopatadine 0.77% was superior to:
    - Vehicle at 24-hour duration-of-action CAC;
    - PATADAY at 24-hour duration-of-action CAC.

For testing three time points within each hypothesis, the Bonferroni correction with a significance level of 0.017 for each time point was used.

- For Study C-12-053,
  - **Step 1**: first test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at the onset-of-action using a significant

level of 5% (2-sided). If the test is statistically significant, proceed to Step 2; otherwise no testing would be performed for the remaining three hypotheses.

- **Step 2**: test the treatment difference in the itching score between Olopatadine 0.77% and the vehicle at 24-hour duration-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 3; otherwise no testing would be performed for the remaining two hypotheses.
- **Step 3**: test the treatment difference in the itching score between Olopatadine 0.77% and PATANOL at 24-hour duration-of-action using a significant level of 5% (2-sided). If the test was statistically significant, proceed to Step 4; otherwise no testing would be performed for the remaining hypothesis.
- **Step 4**: test the treatment difference in the itching score between Olopatadine 0.77% and PATADAY at 24-hour duration-of-action using a significant level of 5% (2-sided).
- For testing three time points within each Step, the Bonferroni correction with a significance level of 0.017 for each time point was used.

It should be noted that the above approaches were conducted post-hoc and only served as a reference for the statistical reviewer to better understand the efficacy results. Comments recommending the above gatekeeping approach were conveyed to the applicant at the protocol design stage; however, the applicant did not follow the recommendation.

For both Study C-10-126 and Study C-12-053 mixed model repeated measures (MMRM) analysis of variance was employed as the primary analysis method. In Study C-10-126, the average of the scores from both eyes was the dependent variable in the model with fixed effects terms for investigator, treatment (Olopatadine 0.77%, PATADAY or Vehicle), time, and treatment-by-time interaction. In Study C-12-053, the score from each eye was the dependent variable in the model with fixed effects terms for investigator, treatment (Olopatadine 0.77%, PATADAY, PATANOL or Vehicle), eye (OD or OS), time, and treatment-by-time interaction.

The applicant was aware of this difference in the dependent variable during protocol design stage for Study C-12-053 and decided to use individual score. According to the applicant, the primary analysis approach used in C-12-053 was a more efficient approach since the analysis was based directly on the score as assessed for each eye and not on summaries; in addition, since the average was a sufficient statistic for the mean parameters of interest, the difference in approach was not expected to materially affect the estimates of within and between-treatment mean parameters. The statistical reviewer considered both approaches acceptable; as expected, the efficacy results using both approaches were consistent.

The applicant also conducted additional analysis of the primary efficacy endpoint for Study C-10-126 using the same model as the one used in Study C-12-053 where dependent variable was individual score from each eye (left or right). Furthermore, additional analysis of the primary efficacy endpoint for Study C-12-053 was conducted by the statistical reviewer using the same model as the one used in Study C-10-126 where dependent variable was the average scores from both eyes for each subject.

The results of both approaches (average score from both eyes as dependent variable, or individual score from each eye as dependent variable) were similar for both studies. To simplify the presentation of the efficacy results for both studies and be consistent, the study results presented in this review were based on using the approach with individual score from each eye as dependent variable.

5.2 Collective Evidence

For Study C-10-126:

- At onset-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.54 (95% CI: [-1.82, -1.25]) at 3 minutes post-CAC; -1.53 (95% CI: [-1.84, -1.22]) at 5 minutes post-CAC; and -1.49 (95% CI: [-1.80, -1.18]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 16-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.50 (95% CI: [-1.77, -1.23]) at 3 minutes post-CAC; -1.48 (95% CI: [-1.79, -1.16]) at 5 minutes post-CAC; and -1.38 (95% CI: [-1.69, -1.07]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.61 (95% CI: [-1.88, -1.33]) at 3 minutes post-CAC; -1.51 (95% CI: [-1.81, -1.21]) at 5 minutes post-CAC; and -1.41 (95% CI: [-1.72, -1.11]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.48 (95% CI: [-0.76, -0.20]) at 3 minutes post-CAC; -0.42 (95% CI: [-0.72, -0.12]) at 5 minutes post-CAC; and -0.41 (95% CI: [-0.72, -0.10]) at 7 minutes post-CAC. The p-values at these three time points were all <0.01.

(b) (4)

- At onset-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.02 (95% CI: [-0.31, 0.26]) at 3 minutes post-CAC; -0.08 (95% CI: [-0.39, 0.22]) at 5 minutes post-CAC; and -0.13 (95% CI: [-0.44, 0.17]) at 7 minutes post-CAC.
- At 16-hour duration-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.17 (95% CI: [-0.44, 0.11]) at 3 minutes post-

CAC; -0.24 (95% CI: [-0.55, 0.07]) at 5 minutes post-CAC; and -0.23 (95% CI: [-0.54, -0.08]) at 7 minutes post-CAC.

For Study C-12-053:

- At onset-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis at all 3 post CAC time points. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.53 (95% CI: [-1.76, -1.30]) at 3 minutes post-CAC; -1.46 (95% CI: [-1.71, -1.22]) at 5 minutes post-CAC; and -1.17 (95% CI: [-1.45, -0.90]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and Vehicle were -1.29 (95% CI: [-1.60, -0.97]) at 3 minutes post-CAC; -1.15 (95% CI: [-1.46, -0.84]) at 5 minutes post-CAC; and -0.89 (95% CI: [-1.22, -0.57]) at 7 minutes post-CAC. The p-values at these three time points were all <0.0001.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATANOL dosed once a day (instead of the approved twice-daily regimen) for the treatment of ocular itching associated with allergic conjunctivitis. The point estimates for the treatment differences between Olopatadine 0.77% and PATANOL were -0.52 (95% CI: [-0.78, -0.27]) at 3 minutes post-CAC; -0.48 (95% CI: [-0.73, -0.23]) at 5 minutes post-CAC; and -0.39 (95% CI: [-0.65, -0.12]) at 7 minutes post-CAC. The p-values at these three time points were all <0.01.
- At 24-hour duration-of-action, Olopatadine 0.77% was superior to PATADAY for the treatment of ocular itching associated with allergic conjunctivitis at 3 and 5 minutes (b) (4) post-CAC. The point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.31 (95% CI: [-0.57, -0.06]; p-value=0.0156) at 3 minutes post-CAC; -0.26 (95% CI: [-0.51, -0.01]; p-value=0.046) at 5 minutes post-CAC; and -0.16 (95% CI: [-0.42, 0.11]; p-value=0.25) at 7 minutes post-CAC.

(b) (4)

- At onset-of-action, the point estimates for the treatment differences between Olopatadine 0.77% and PATADAY were -0.09 (95% CI: [-0.28, 0.09]) at 3 minutes post-CAC; -0.08 (95% CI: [-0.29, 0.12]) at 5 minutes post-CAC; and 0.04 (95% CI: [-0.18, 0.26]) at 7 minutes post-CAC.

Table 21: Study C-10-126 Analysis of Ocular Itching Score* (ITT)

	Onset-of-Action			16-Hour Duration-of-Action			24-Hour Duration-of-Action		
	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)	Olop 0.77% (N=66)	PATADAY (N=68)	Vehicle (N=68)
3 Minutes	0.36	0.39	1.90	0.70	0.87	2.20	0.93	1.41	2.54
Difference		-0.02	-1.54		-0.17	-1.50		-0.48	-1.61
(95% CI)		(-0 31, 0.26)	(-1.82, -1.25)		(-0.44, 0.11)	(-1.77, -1.23)		(-0.76, -0.20)	(-1.88, -1.33)
5 Minutes	0.53	0.61	2.06	0.79	1.04	2.27	1.10	1.52	2.62
Difference		-0.08	-1.53		-0.24	-1.48		-0.42	-1.51
(95% CI)		(-0 39, 0.22)	(-1.84, -1.22)		(-0.55, 0.07)	(-1.79, -1.16)		(-0.72, -0.12)	(-1.81, -1.21)

7 Minutes	0.48	0.61	1.97	0.75	0.98	2.13	1.09	1.50	2.50
Difference		-0 13	-1.49		-0.23	-1.38		-0.41	-1.41
(95% CI)		(-0.44, 0.17)	(-1.80, -1.18)		(-0.54, 0.08)	(-1.69, -1.07)		(-0.72, -0.10)	(-1.72, -1.11)
Average	0.46	0.54	1.98	0.75	0.96	2.20	1.04	1.48	2.55
Difference		-0.08	-1.51		-0.21	-1.45		-0.44	-1.51
(95% CI)		(-0 37, 0.21)	(-1.81, -1.23)		(-0.49, 0.07)	(-1.73, -1.17)		(-0.72, -0.16)	(-1.79, -1.24)

* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.
Source: Tables 2.7.3.2-2, 2.7.3.2-3, and 2.7.3.2-7 of Summary of Clinical Efficacy.

Table 22: Study C-12-053 Analysis of Ocular Itching Score* (ITT)

	Onset-of-Action				24-Hour Duration-of-Action			
	Olopatadine 0.77% (N=98)	PATADAY (N=99)	PATANOL[1] (N=99)	Vehicle (N=49)	Olopatadine 0.77% (N=98)	PATADAY (N=99)	PATANOL[1] (N=99)	Vehicle (N=49)
3 Minutes	0.38	0.47	0.59	1.91	1.01	1.33	1.53	2.30
Difference		-0.09	-0.21	-1.53		-0.31	-0.52	-1.29
(95% CI)		(-0.28, 0.09)	(-0.40, -0.02)	(-1.76, -1.30)		(-0.57, -0.06)	(-0.78, -0.27)	(-1.60, -0.97)
5 Minutes	0.53	0.61	0.79	1.99	1.22	1.48	1.70	2.37
Difference		-0.08	-0.26	-1.46		-0.26	-0.48	-1.15
(95% CI)		(-0.29, 0.12)	(-0.47, -0.06)	(-1.71, -1.22)		(-0.51, -0.01)	(-0.73, -0.23)	(-1.46, -0.84)
7 Minutes	0.65	0.61	0.83	1.82	1.25	1.41	1.64	2.14
Difference		0.04	-0.18	-1.17		-0.16	-0.39	-0.89
(95% CI)		(-0.18, 0.26)	(-0.41, 0.04)	(-1.45, -0.90)		(-0.42, 0 11)	(-0.65, -0.12)	(-1.22, -0.57)
Average	0.52	0.56	0.74	1.91	1.16	1.40	1.62	2.27
Difference		-0.05	-0.22	-1.39		-0.24	-0.46	-1.11
(95% CI)		(-0.24, 0.14)	(-0.41, -0.03)	(-1.62, -1.16)		(-0.48, -0.00)	(-0.70, -0.23)	(-1.40, -0.82)

* Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.
[1] PATANOL was dosed only once (instead of the approved twice-a-day regimen) at Visit 3A (for 24-hour duration-of-action) and Visit 4 (onset-of-action).
Source: Tables 2.7.3.2-10, and 2.7.3.2-11 of Summary of Clinical Efficacy.

5.3 Conclusions and Recommendations

Although in Study C-12-053, (b) (4) the study results were consistent between Study C-12-053 and Study C-10-126 and all in favor of Olopatadine 0.77%. In addition, in both studies, comparing with Vehicle, the ocular itching treatment effects of Olopatadine 0.77% were highly significant (p-value<0.0001) at all three time points in all the study visits. Therefore, this reviewer concluded that there is enough evidence to support the efficacy of Olopatadine 0.77% for the treatment of ocular itching associated with allergic conjunctivitis and recommended its approval for this indication.

5.4 Labeling Recommendations

The applicant's proposal (the first portion) for Section 14 is as follows:

14 CLINICAL STUDIES

(b) (4)

Table 1 (b) (4) **Itching Scores by Treatment Group and Treatment Difference in Mean Itching**

(b) (4)

(b) (4)

(b) (4)

The applicant also included (b) (4).

The rationale for the statistical reviewer's labeling recommendations was:

- Since the results of the two individual studies clearly illustrated the efficacy of Olopatadine 0.77% for the treatment of ocular itching, the statistical reviewer recommended that (b) (4).
- The approved regimen for PATANOL was twice daily; however, in Study C-12-053 that comparing Olopatadine 0.77% with PATANOL at 24-hour duration-of-action, PATANOL was dosed for only once (instead of the approved twice-a-day regimen) in the previous day. (b) (4)

The statistical reviewer recommended that studies' results be presented as follows for Section 14 CLINICAL STUDIES of the labeling:

** Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.*
The ocular itching score range is 0-4, where 0 is none and 4 is incapacitating itch.

The protocol-defined primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC at all the study visits; while the above table presented the mean itching scores of the three time points at each study visit, which were not protocol-defined primary efficacy endpoints. As an alternative option, in addition to the mean itching scores, the statistical reviewer recommended that studies' results be presented as the following table to reflect precisely the primary efficacy endpoints as defined in the study protocol:

Itching Scores by Treatment Group and Treatment Difference in Mean Itching*

	Time Point	**#TRADENAME# Olopatadine, 0.77%**	**PATADAY** (Olopatadine, 0.2%)		**Vehicle**	
Study 1		(N = 66)	(N = 68)		(N = 68)	
		Mean	Mean	Difference (95% CI)*	Mean	Difference (95% CI)*
Onset	**Average**	0.46	0.54	-0.08 (-0.37, 0.21)	1.98	-1.51 (-1.81, -1.23)
	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)	1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)	2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)	1.97	-1.49 (-1.80, -1.18)
16h	**Average**	0.75	0.96	-0.21 (-0.49, 0.07)	2.20	-1.45 (-1.73, -1.17)

	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)	2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)	2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)	2.13	-1.38 (-1.69, -1.07)
24h	**Average**	1.04	1.48	-0.44 (-0.72, -0.16)	2.55	-1.51 (-1.79, -1.24)
	3 mins	0.93	1.41	-0.48 (-0.76, -0.20)	2.54	-1.61 (-1.88, -1.33)
	5 mins	1.10	1.52	-0.42 (-0.72, -0.12)	2.62	-1.51 (-1.81, -1.21)
	7 mins	1.09	1.50	-0.41 (-0.72, -0.10)	2.50	-1.41 (-1.72, -1.11)
Study 2		(N = 98)	(N = 99)		(N = 49)	
Onset	**Average**	0.52	0.56	-0.05 (-0.24, 0.14)	1.91	-1.39 (-1.62, -1.16)
	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)	1.82	-1.17 (-1.45, -0.90)
24h	**Average**	1.16	1.40	-0.24 (-0.48, -0.00)	2.27	-1.11 (-1.40, -0.82)
	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	2.14	-0.89 (-1.22, -0.57)

** Mean score estimates, treatment differences and corresponding 95% confidence intervals (CIs) were based on analysis of repeated measures using a mixed model with itching scores from each eye (left or right) as the dependent variable and fixed effect terms for investigator, treatment, eye-type (left or right), time, and treatment-by-time interaction.*
The ocular itching score range is 0-4, where 0 is none and 4 is incapacitating itch.

Although this statistical reviewer preferred the table with results of each time point to be used for the clinical studies section as it presented details of the protocol-defined primary efficacy endpoints, the statistical reviewer also realized that it was a relatively long table. Therefore, the statistical reviewer would like to defer the final decision of which table to present to the clinical review team based on their consideration of clinical relevance.

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/s/

YUNFAN DENG
01/02/2015

YAN WANG
01/02/2015
I concur.