



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 208694
Supplement #: 0000
Drug Name: Zerviate™ (Cetirizine Ophthalmic Solution, 0.24%)
Indication(s): Treatment of ocular itching associated with allergic conjunctivitis
Applicant: Nicox Ophthalmics, Inc.
Date(s): Submitted: 04/18/2016
PDUFA date: 10/18/2016
Review Priority: Priority

Biometrics Division: DBIV
Statistical Reviewer: Yunfan Deng, Ph.D.
Concurring Reviewers: Yan Wang, Ph.D.

Medical Division: Division of Transplant and Ophthalmology Products
Clinical Team: Lucious Lim, MD
William Boyd, MD, Team Leader
Project Manager: June Germain

Keywords: ocular itching, conjunctival redness, allergic conjunctivitis

Table of Contents

1	EXECUTIVE SUMMARY	4
2	INTRODUCTION	6
2.1	OVERVIEW	6
2.1.1	<i>Drug Class and Indication</i>	6
2.1.2	<i>History of Drug Development</i>	7
2.1.3	<i>Studies Reviewed</i>	7
2.2	DATA SOURCES	8
3	STATISTICAL EVALUATION	9
3.1	DATA AND ANALYSIS QUALITY	9
3.2	EVALUATION OF EFFICACY	9
3.2.1	<i>Study Design and Endpoints</i>	9
3.2.2	<i>Statistical Methodologies</i>	13
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	14
3.2.3.1	Study 11-100-0012	14
3.2.3.2	Study 12-100-0006	15
3.2.3.3	Study 13-100-0002	16
3.2.4	<i>Results and Conclusions</i>	18
3.2.4.1	Ocular Itching Scores	18
3.2.4.2	Conjunctival Redness Scores	22
3.2.4.3	Overall Conclusion	23
3.3	EVALUATION OF SAFETY	24
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	25
4.1	GENDER, RACE, AND AGE	25
5	SUMMARY AND CONCLUSIONS	28
5.1	STATISTICAL ISSUES	28
5.2	COLLECTIVE EVIDENCE	28
5.3	CONCLUSIONS AND RECOMMENDATIONS	30
5.4	LABELING RECOMMENDATIONS	31

LIST OF TABLES

Table 1: Summary of Ocular Itching Scores (ITT, LOCF)	4
Table 2: Summary of Conjunctival Redness Scores (ITT, LOCF).....	5
Table 3: Summary of Efficacy Studies for Cetirizine.....	8
Table 4: Schedule of Assessment	11
Table 5: Ocular Itching Assessment Grades.....	12
Table 6: Conjunctival Redness Assessment Grades	12
Table 7: Study 11-100-0012 Subjects' Disposition.....	14
Table 8: Study 11-100-0012 Demographic and Baseline Characteristics (ITT)	14
Table 9: Study 12-100-0006 Subjects' Disposition.....	15
Table 10: Study 12-100-0006 Demographic and Baseline Characteristics (ITT)	16
Table 11: Study 13-100-0002 Subjects' Disposition.....	16
Table 12: Study 13-100-0002 Demographic and Baseline Characteristics (ITT)	17
Table 13: Ocular Itching Scores by Treatment Group and Treatment Difference (ITT, LOCF)	19
Table 14: Summary of Patients Discontinuation (Studies 11-100-0012, 12-100-0006, and 13-100-0002).....	20
Table 15: Ocular Itching Scores by Treatment Group and Treatment Difference (ITT, BOCF)	20
Table 16: Percentage of Subjects with 1 Unit Improvement from Baseline in Ocular Itching Scores at Each Post-CAC Time Point (ITT, BOCF).....	21
Table 17: Conjunctival Redness Scores by Treatment Group and Treatment Difference (ITT, LOCF).....	22
Table 18: Percentage of Subjects with 0.5 Unit Improvement from Baseline in Conjunctival Redness Scores at Each Post-CAC Time Point (ITT, BOCF).....	23
Table 19: P-values for Ocular Itching Scores by Time Point and Study Visit (ITT, LOCF)	24
Table 20: Summary of Treatment-Emergent Adverse Events (Studies 11-100-0012, 12-100-0006, and 13-100-0002, Safety Analysis Set).....	24
Table 21: Study 11-100-0012 Ocular Itching Scores Subgroup Analyses (ITT, LOCF).....	25
Table 22: Study 12-100-0006 Ocular Itching Scores Subgroup Analyses (ITT, LOCF).....	26
Table 23: Study 13-100-0002 Ocular Itching Scores Subgroup Analyses (ITT, LOCF).....	27
Table 24: Summary of Ocular Itching Scores (ITT, LOCF)	28
Table 25: Summary of Conjunctival Redness Scores (ITT, LOCF).....	29
Table 26: Percentage of Subjects with 1 Unit Improvement from Baseline in Ocular Itching Scores at Each Post-CAC Time Point (ITT, BOCF).....	30

LIST OF FIGURES

Figure 1: Study design schematic	11
--	----

1 EXECUTIVE SUMMARY

This NDA seeks approval of cetirizine ophthalmic solution, 0.24% dosed twice daily for the treatment of ocular itching associated with allergic conjunctivitis. Although the FDA had approved oral cetirizine hydrochloride (Zyrtec®; Pfizer; in various form and strength) for the relief of symptoms associated with perennial allergic rhinitis and uncomplicated skin manifestations of chronic idiopathic urticarial in children 6 months of age and older, this NDA was granted a priority 6-month review under the Best Pharmaceuticals for Children Act (CDER MaPP 6020.3; June 25, 2013) since the applicant evaluated the safety of cetirizine ophthalmic solution, 0.24% in pediatric patients 2 years of age and older.

The efficacy of cetirizine ophthalmic solution, 0.24% (abbreviated as “cetirizine” throughout this review) was evaluated in three pivotal studies: two multicenter studies 11-100-0012 and 13-100-0002, and one single-center study 12-100-0006. The three studies were randomized, double-masked, vehicle-controlled, parallel-group studies. They used the conjunctival allergen challenge (CAC) model to evaluate the onset and duration of action of cetirizine for the treatment of acute allergic conjunctivitis. These studies were almost identical in design except for the timing of duration-of-action evaluation. The onset of action was evaluated 15 minutes after study treatment instillation; and the duration of action was measured using CAC at 8 hours (in Studies 13-100-0002 and 12-100-0006) or 16 hours (in Study 11-100-0012) after study treatment instillation.

The co-primary efficacy variables were ocular itching scores and conjunctival redness scores for these three studies. Ocular itching was subject-evaluated on a five-point scale (0 to 4, 0.5 unit increments were allowed) at 3, 5, and 7 minutes post CAC; and conjunctival redness was investigator-evaluated on a five-point scale (0 to 4, 0.5 unit increments were allowed) at 7, 15, and 20 minutes post CAC.

For the primary efficacy endpoint of ocular itching scores, the three studies demonstrated statistical superiority of cetirizine to vehicle at both the onset and duration-of-action evaluations (Table 1). At 15-minute onset-of-action evaluation, the mean itching score for cetirizine ranged from 0.71 to 1.18, and for vehicle ranged from 2.10 to 2.54; the treatment difference ranged from -1.00 to -1.53 with p-values <0.0001 at each of the post-CAC time point (3-, 5-, and 7-minute). At the 8-hour duration-of-action evaluation, the mean itching score for cetirizine ranged from 1.54 to 2.03, and for vehicle ranged from 2.53 to 2.94; the treatment difference ranged from -0.84 to -0.99 with p-values <0.0001 at each of the post-CAC time point. At the 16-hour duration-of-action evaluation, the mean itching score for cetirizine ranged from 1.71 to 1.88, and for vehicle ranged from 2.22 to 2.50; the treatment difference ranged from -0.46 to -0.64 with p-values <0.0184 for at each of the post-CAC time point.

Table 1: Summary of Ocular Itching Scores (Intent-to-Treat [ITT], Last Observation Carried Forward [LOCF])

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹ p-value ²			
				Time Post-CAC			Time Post-CAC			
				3 min	5 min	7 min	3 min	5 min	7 min	

11-100-0012	Cetirizine	46/44	15 min	0.71	1.01	1.00	-1.47	-1.31	-1.10
	Vehicle	45/45		2.18	2.31	2.10	(-1.82, -1.12)	(-1.66, -0.95)	(-1.48, -0.72)
	Cetirizine	46/44	16 hours	1.71	1.88	1.76	-0.64	-0.62	-0.46
	Vehicle	45/45		2.34	2.50	2.22	(-0.95, -0.33)	(-0.95, -0.29)	(-0.84, -0.08)
12-100-0006	Cetirizine	50/49	15 min	1.00	1.18	1.11	-1.38	-1.25	-1.00
	Vehicle	50/47		2.38	2.43	2.11	(-1.72, -1.05)	(-1.58, -0.91)	(-1.35, -0.65)
	Cetirizine	50/49	8 hours	1.76	1.85	1.54	-0.93	-0.89	-0.99
	Vehicle	50/47		2.69	2.74	2.53	(-1.26, -0.61)	(-1.24, -0.54)	(-1.40, -0.59)
13-100-0002	Cetirizine	51/43	15 min	1.01	1.17	1.15	-1.53	-1.34	-1.07
	Vehicle	50/44		2.54	2.51	2.23	(-1.92, -1.15)	(-1.71, -0.97)	(-1.46, -0.69)
	Cetirizine	51/43	8 hours	1.94	2.03	1.82	-0.92	-0.90	-0.84
	Vehicle	50/44		2.86	2.94	2.66	(-1.25, -0.58)	(-1.23, -0.57)	(-1.21, -0.48)

* Post study treatment instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

² P-value calculated using a two-sample t-test comparing active treatment to vehicle at each individual time point.

Source: Table 5 of Summary of Clinical Efficacy, Table 9 of Study 11-100-0012 Report, Table 9 of Study 12-100-0006 Report, and Tables 9 and 10 of Study 13-100-0002 Report.

For the primary efficacy endpoint of conjunctival redness scores, studies 11-100-0012 and 12-100-0006 failed to demonstrate statistical superiority of cetirizine to vehicle at both the onset- and duration-of-action evaluations. Study 13-100-0002 failed to demonstrate statistical superiority of cetirizine to vehicle at onset-of-action evaluation; at the 8-hour duration-of-action evaluation in this study, conjunctival redness scores were significantly lower in the cetirizine group compared to vehicle group.

Table 2: Summary of Conjunctival Redness Scores (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹		
				Time Post-CAC			Time Post-CAC		
				7 min	15 min	20 min	7 min	15 min	20 min
11-100-0012	Cetirizine	46/44	15 min	2.02	2.23	2.28	-0.03	0.09	0.10
	Vehicle	45/45		2.05	2.13	2.18	(-0.34, 0.27)	(-0.20, 0.39)	(-0.19, 0.40)
	Cetirizine	46/44	16 hours	1.72	1.96	1.92	-0.22	-0.06	-0.06
	Vehicle	45/45		1.94	2.02	1.98	(-0.55, 0.11)	(-0.39, 0.27)	(-0.38, 0.26)
12-100-0006	Cetirizine	50/49	15 min	1.66	1.93	1.95	-0.33	-0.03	-0.01
	Vehicle	50/47		1.98	2.09	2.09	(-0.53, -0.06)	(-0.26, 0.19)	(-0.26, 0.23)
	Cetirizine	50/49	8 hours	1.97	2.30	2.30	-0.30	-0.03	-0.01
	Vehicle	50/47		2.27	2.34	2.32	(-0.53, -0.06)	(-0.26, 0.19)	(-0.26, 0.23)
13-100-0002	Cetirizine	51/43	15 min	1.92	2.19	2.15	-0.46	-0.18	-0.25
	Vehicle	50/44		2.38	2.37	2.41	(-0.73, -0.19)	(-0.43, 0.07)	(-0.51, 0.00)
	Cetirizine	51/43	8 hours	1.97	2.13	2.09	-0.42	-0.24	-0.31
	Vehicle	50/44		2.39	2.38	2.40	(-0.68, -0.16)	(-0.49, 0.00)	(-0.58, -0.05)

* Post study treatment instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Source: Table 6 of Summary of Clinical Efficacy.

The three studies failed to demonstrate a statistically significant treatment effect in conjunctival redness scores. However, based on the p-values of ocular itching scores comparing cetirizine versus vehicle at each post-CAC time point for the onset- and duration-of-action efficacy evaluations (Table 1), if the applicant had split the 0.05 alpha level between the two co-primary efficacy endpoints (0.025 alpha level for ocular itching scores and 0.025 alpha level for conjunctival redness scores), all three studies would still have had demonstrated statistical superiority of cetirizine to vehicle at each post-CAC time point (3-, 5-, and 7-minute) for the onset- and duration-of-action visits in ocular itching scores (all p-values < 0.025).

Therefore, the statistical reviewer concluded that there was substantial statistical evidence to support the superiority of cetirizine to vehicle in terms of ocular itching scores.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

The following are excerpts from 7.0 Introduction of Study 11-100-0012 Report:

“Allergies are relatively common among the general population, affecting >15% of the global population and as much as 30% of the US population. Allergic responses can be triggered by a variety of stimuli, including tree and grass pollens, animal hair and dander, and other environmental insults. Ocular symptoms include itching, redness, chemosis, tearing, and eyelid swelling. Allergic reactions can vary from a mild, self-limiting disease to a debilitating condition that significantly impairs the quality of life of allergen-responsive individuals.

The physiologic basis for allergic conjunctivitis is multifactorial and involves both an early acute phase triggered by mast cell degranulation and release of histamine and a late phase involving various pro-inflammatory mediators. Histamine is the primary mediator responsible for the typical early phase reaction that triggers itching, vasodilation and vascular leaking leading to ocular redness, chemosis, and blepharitis. Mast cells synthesize and release cytokines, chemokines, and growth factors that initiate a cascade of inflammatory events leading to a late phase reaction characterized by recruitment of eosinophils, neutrophils, and subsequent lymphocytes and macrophages in the conjunctival tissues.

Most of the approved treatments for ocular allergy are antihistamines, mast cell stabilizers, or both, and act to reduce the signs and symptoms of the early phase reaction. Cetirizine hydrochloride is an orally active antihistamine. Its principal effects are mediated via selective inhibition of H1 histamine receptors.”

2.1.2 History of Drug Development

Since 1995, the FDA had approved oral cetirizine hydrochloride (Zyrtec®; Pfizer; tablets, chewable tablets, and syrup formulation in various strength) for the relief of symptoms associated with perennial allergic rhinitis and uncomplicated skin manifestations of chronic idiopathic urticarial in children 6 months of age and older. The FDA also approved Zyrtec® tablet, chewable tablet and syrup formulation for over-the-counter use in 2007. According to the applicant, [REDACTED] (b) (4)

The applicant developed an ophthalmic solution of cetirizine for relief of ocular itching [REDACTED] (b) (4) associated with allergic conjunctivitis. The majority of original studies conducted by the applicant were performed under IND 108558. Under IND 108558, [REDACTED] (b) (4)

[REDACTED] Based on the results of a dose ranging study, the applicant decided that cetirizine 0.24% was the optimal dose concentration. Subsequently, four studies (three safety and efficacy, and one safety; see Section 2.1.3 below for details) were conducted using the final proposed commercial formulation of cetirizine ophthalmic solution, 0.24%.

For final formulation of cetirizine 0.24%, the first safety and efficacy pivotal study conducted was Study 11-100-0012 and followed by Study 12-100-0006. The duration-of-action evaluation time was 16 hours post study treatment in Study 11-100-0012; while it was 8 hours in Study 12-100-0006. In the face-to-face meeting with the Agency in March 2013, the agency commented that based on the summary information provided in the meeting package, it appeared that the effect of cetirizine on ocular itching had worn off by 16 hours post-treatment and was only marginally effective 8 hours post-treatment; the Agency recommended that an additional study be conducted which demonstrates continued efficacy at 8 hours in order for cetirizine to be labeled as twice-daily (BID) dosing. Therefore, the applicant conducted an additional pivotal study (Study 13-100-0002) which evaluated duration of action for cetirizine at 8 hours post-treatment and sought the approval of cetirizine for BID dosing in this NDA submission.

2.1.3 Studies Reviewed

As discussed in previous section, the efficacy of cetirizine 0.24% was evaluated in three pivotal studies: two multicenter studies 11-100-0012 and 13-100-0002, and one single-center study 12-100-0006.

The three efficacy studies were identical in design except for the timing of evaluating duration-of-action. All the three studies were randomized, double-masked, and vehicle-controlled, parallel-group studies that used conjunctival allergen challenge (CAC) model to evaluate the onset and duration-of-action of cetirizine for the treatment of acute allergic conjunctivitis.

Table 3: Summary of Efficacy Studies for Cetirizine

Study No	Design	Objective	Treatment Groups Randomized/Completed	Study Population
11-100-0012	Multi-center, randomized, double masked, 2-arm	to evaluate the efficacy and safety of cetirizine ophthalmic solution, 0.24% compared with vehicle in the prevention of allergen-induced conjunctivitis using the conjunctival allergen challenge (CAC) model	Cetirizine : 46/44 Vehicle: 45/45	Subjects 10 years or older with a prior history of ocular allergies
12-100-0006	Single-center, randomized, double masked, 2-arm	to evaluate the efficacy and safety of cetirizine ophthalmic solution, 0.24% compared with vehicle in the prevention of allergen-induced conjunctivitis using the conjunctival allergen challenge (CAC) model	Cetirizine : 50/49 Vehicle: 50/47	Subjects 10 years or older with a prior history of ocular allergies
13-100-0002	Multi-center, randomized, double masked, 2-arm	to evaluate the efficacy and safety of cetirizine ophthalmic solution, 0.24% compared with vehicle in the prevention of allergen-induced conjunctivitis using the conjunctival allergen challenge (CAC) model	Cetirizine : 51/43 Vehicle: 50/44	Subjects 10 years or older with a prior history of ocular allergies

Source: Table 3 of Summary of Clinical Efficacy.

The applicant also conducted a multi-center, double-masked, randomized, vehicle-controlled, parallel-group safety study (Study 14-100-0006) to evaluate the safety of cetirizine ophthalmic solution, 0.24% used twice daily in healthy adult subjects and in pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis). Since this study investigated the safety of cetirizine in pediatric subjects as young as 2 years old, this NDA submission was granted as a priority 6-month review under the Best Pharmaceuticals for Children Act (CDER MaPP 6020.3; June 25, 2013). This statistical review will not focus on this safety study.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies 11-100-0012, 12-100-0006, and 13-100-0002. The study reports are available at:

<\\cdsesub1\evsprod\NDA208694\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-allergic-conjunctivitis\5351-stud-rep-contr\study-11-100-0012>

<\\cdsesub1\evsprod\NDA208694\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-allergic-conjunctivitis\5351-stud-rep-contr\study-12-100-0006>

<\\cdsesub1\evsprod\NDA208694\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-allergic-conjunctivitis\5351-stud-rep-contr\study-13-100-0002>

The applicant submitted SAS datasets electronically; the datasets for the three studies are available respectively at:

<\\cdsesub1\evsprod\NDA208694\0001\m5\datasets\11-100-0012>

<\\cdsesub1\evsprod\NDA208694\0001\m5\datasets\12-100-0006>

<\\cdsesub1\evsprod\NDA208694\0001\m5\datasets\13-100-0002>

The SAS program codes that were used to generate the results in the study reports are available respectively at:

<\\cdsesub1\evsprod\NDA208694\0006\m5\datasets\11-100-0012\analysis\adam\programs>

<\\cdsesub1\evsprod\NDA208694\0006\m5\datasets\12-100-0006\analysis\adam\programs>

<\\cdsesub1\evsprod\NDA208694\0006\m5\datasets\13-100-0002\analysis\adam\programs>

The ocular itching scores were included in the “adals.xpt” dataset with variable names “AVAL”. The conjunctival redness scores were included in the “adali.xpt” dataset with variable names “AVAL”. The treatment variable, given both as numeric (TRTAN) and character (TRTA), was also included in both the above datasets. The adverse events were included in the “adae.xpt” dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The three efficacy studies 11-100-0012, 13-100-0002, and 12-100-0006 were almost identical in design, except that:

- 11-100-0012 and 13-100-0002 were multi-center studies and 12-100-0006 was a single-center study;
- For the duration-of-action evaluation, studies 11-100-0012 were performed at 16 hours post study treatment instillation while both studies 12-100-0006 and 13-100-0002 were performed at 8 hours post study treatment instillation.

All the three studies were randomized, double-masked, vehicle-controlled, and parallel-group studies that used conjunctival allergen challenge (CAC) model to evaluate the onset and duration of action of cetirizine ophthalmic solution 0.24% for the treatment of acute allergic

conjunctivitis. The human CAC model utilizes a specific ocular allergen to initiate a reproducible inflammatory response consistent with the signs and symptoms of allergic conjunctivitis. The CAC model was used bilaterally at Visit 1 (Day -21), Visit 2 (Day -14), Visit 3B (Day 0), and Visit 4 (Day 14) to induce subjects' allergic conjunctivitis signs and symptoms.

All three studies recruited subjects with a prior history of ocular allergies, which reflects a population most likely to demonstrate a treatment effect for an antiallergic test agent. Specifically, the protocol-defined key inclusion criteria were:

- Was at least 10 years of age of either sex and any race;
- Had a positive history of ocular allergies and a positive skin test reaction to cat dander, dog dander, dust mites, cockroach, grasses, ragweed, and/or trees within the past 24 months;
- Had a calculated best-corrected visual acuity of 0.7 logMar or better in each eye as measured using an ETDRS (Early Treatment Diabetic Retinopathy Study) chart;
- Had a positive bilateral CAC reaction (≥ 2 for itching and ≥ 2 for conjunctival redness) within 10 minutes of instillation of the last titration of allergen at Visit 1;
- Had a positive bilateral CAC reaction (≥ 2 for itching and ≥ 2 for conjunctival redness) for at least two out of three time points at Visit 2;
- Was able and willing to avoid all disallowed medication for the appropriate washout period (5 weeks) and during the study.

For the three studies, there were four study visits as mentioned above. Protocol defined visit schedule were summarized as follows.

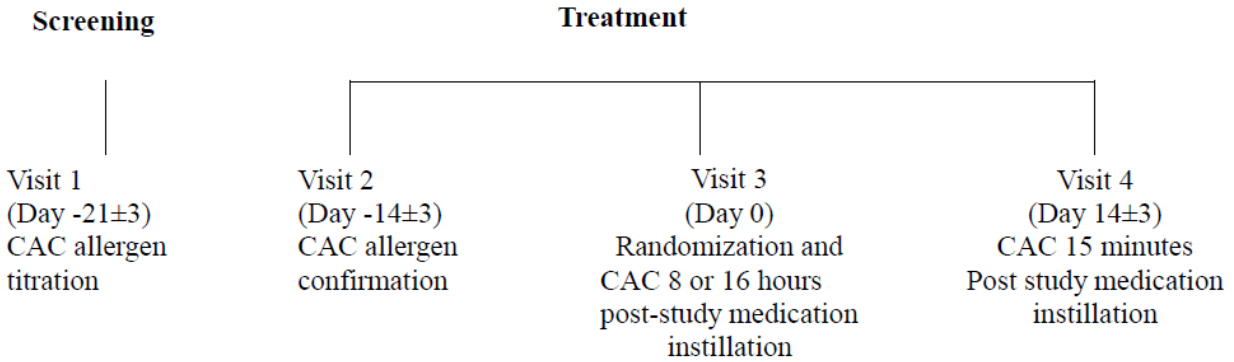
Visit 1 (Day -21 \pm 3; Allergan Titration Visit): subjects' eligibility for trial participation was determined at this study visit. Any subject who failed to test positively to an allergen at Visit 1 was excluded from the study. A positive CAC response was defined as scores of ≥ 2 for both ocular itching and conjunctival redness within 10 minutes of receiving the allergen dose.

Visit 2 (Day -14 \pm 3): subjects underwent a confirmatory CAC at this study visit. If a subject failed to react positively in both eyes in at least two out of the three time points within the 20-minute interval at Visit 2, he/she was excluded from the study.

Visit 3 (Day 0): this visit occurred in two parts. Eligible subjects were randomized at 1:1 ratio to one of the two treatment arms (cetirizine or vehicle) at **Visit 3A** and received their first dose of study treatment in each eye. At **Visit 3B** (16 hours after Visit 3A study medication instillation for Study 11-100-0012; 8 hours after Visit 3A study medication instillation for Studies 12-100-0006 and 13-100-0002), subjects returned to the study site and underwent the CAC. Ocular and nasal signs and symptoms were assessed before and after the CAC.

Visit 4 (Day 14 \pm 3): Subjects received a second dose of study medication, and 15 minutes later received CAC. Ocular and nasal signs and symptoms were assessed. Subjects exited the study at Visit 4.

Figure 1: Study design schematic



Source: Figure 1 of Summary of Clinical Efficacy

For CAC at each visit, ocular itching was assessed by subjects at 3, 5, and 7 minutes after allergen challenge. Conjunctival redness and chemosis were assessed by the Investigator at 7, 15, and 20 minutes after allergen challenge. Lid swelling, tearing/watery eyes, and nasal symptoms were assessed by the subject at 7, 15, and 20 minutes after allergen challenge. The schedule for study visits and the measurements performed at each study visit are presented in the following table.

Table 4: Schedule of Assessment

Evaluation ^a	Visit 1 (Day -21 ± 3)	Visit 2 (Day -14 ± 3)	Visit 3 (Day 0)		Visit 4 (Day 14 ± 3)
			3A	3B	
Informed Consent/Assent/HIPAA	X				
Demographic Data	X				
Medical and Medication History	X				
Pregnancy Test (for females of childbearing potential)	X	X ¹	X ¹	X ¹	X
Medical and Medication History Update		X	X	X	X
Visual Acuity	X	X	X	X	X ²
Slit Lamp Biomicroscopy	X	X	X	X	X ²
Assessment of Ocular & Nasal Signs & Symptoms	X	X	X	X	X
Screening Conjunctival Allergen Challenge	X	X			
Randomization of study subjects			X		
Study Medication Instillation			X ³		X ⁴
In-Office Drop Comfort Assessments ⁵			X		
Drop Efficacy Conjunctival Allergen Challenge				X ⁶	X ⁷
Dilated funduscopy ⁸	X				X
Instillation of Relief Drops ⁹	X	X		X	X
Adverse Event Query			X	X	X

Exit from study					X
-----------------	--	--	--	--	---

¹ For females who were premenarchal at the previous Visit and became menarchal thereafter

² Performed pre-CAC and post-CAC as part of the safety exit exam

³ For Study 11-100-0012, sixteen (16) hours (+1 hour) before Visit 3B CAC; for Studies 0006 and 0002, eight (8) hours (+1 hour) before Visit 3B CAC

⁴ Fifteen (15) minutes pre-CAC

⁵ Includes comfort (immediately, 1 and 2 minutes post-instillation) and drop descriptor word queries (3 minutes post-instillation)

⁶ For Study 11-100-0012, sixteen (16) hours (+1 hour) post-instillation; for Studies 0006 and 0002, eight (8) hours (+1 hour) post-instillation.

⁷ Fifteen (15) minutes post-instillation

⁸ Dilated funduscopy will be performed following CAC assessments.

⁹ Relief drops administered at Visit 1 and may be administered at Visits 2, 3B, and 4 after all assessments are complete. Instillation information must be recorded on the concomitant medication page.

Source: Table 4 of Study 11-100-0012 Report, Table 4 of Study 12-100-0006 Report, and Table 4 of Study 13-100-0002 Report.

For the three studies, the co-primary efficacy endpoints were assessments of ocular itching and conjunctival redness, as follows:

Ocular Itching: At Visits 3B and 4, subjects self-assessed ocular itching in each eye at 3(±1), 5(±1), and 7(±1) minutes post-challenge.

Table 5: Ocular Itching Assessment Grades

Score	Ocular Itching Descriptor
0	None
0.5	An intermittent tickle sensation possible localized in the corner of the eye
1.0	An intermittent tickle sensation involving more than just the corner of the eye
1.5	Intermittent all-over tickling sensation
2.0	A mild continuous itch (can be localized) without desire to rub
2.5	Moderate, diffuse continuous itch with desire to rub
3.0	A severe itch with desire to rub
3.5	Severe itch improved with minimal rubbing
4.0	Incapacitating itch with an irresistible urge to rub

Source: Table 1 of Summary of Clinical Efficacy.

Conjunctival Redness: At Visits 3B and 4, the investigator assessed conjunctival redness in each eye at 7(±1), 15(±1), and 20(±1) minutes post-challenge.

Table 6: Conjunctival Redness Assessment Grades

Score	Ocular Itching Descriptor
0	None
1	Mild: slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal
2	Moderate: more apparent dilation of blood vessels; vessel color is more intense (redder); involves the majority of the vessel bed
3	Severe: numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quadrantic
4	Extremely severe: large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed

Source: Table 2 of Summary of Clinical Efficacy.

The unit of analysis for all ocular variables was the average of both eyes of each subject.

The sample size estimation of 90 to 100 subjects (45 to 50 subjects per group) for the three studies was based on the following assumptions proposed by the applicant to support the primary efficacy endpoints:

- 0.05 two-sided level of significance.
- 1.0 mean difference in ocular itching or conjunctival redness between study drug and vehicle.
- Standard deviation of 0.95 for both endpoints.
- 99% power

3.2.2 Statistical Methodologies

All three studies (11-100-0012, 13-100-0002, and 12-100-0006) intended to demonstrate the superiority of cetirizine to vehicle in ocular itching and conjunctival redness based on the scores of ocular itching and conjunctival redness at Visit 3B and Visit 4. According to the protocol-defined clinical criteria for efficacy, to demonstrate efficacy at a visit, cetirizine needed to show clinical superiority over vehicle by a mean difference (based on point estimator) of at least 0.5 units of a 5 point scale for all post-CAC time points, and by at least 1 unit for the majority of the post-CAC time points (i.e. 2 out of 3) for both primary efficacy variables of ocular itching and conjunctival redness.

For all three studies, there were three different analysis populations (also known as analysis sets) defined by the applicant:

- **Intent-to-Treat (ITT) population**, which included all randomized subjects. The ITT population was analyzed as randomized and used for the efficacy analyses.
- **Per-Protocol (PP) Population**, which included all randomized subjects who completed the study with no major protocol violations. This population was analyzed by the applicant as treated using observed data only for confirmatory analyses.
- **Safety analysis set**, which included all randomized subjects who received at least one dose of study treatment. The safety population was analyzed as treated and used for the safety analyses. No data were to be excluded for any reason.

The primary efficacy analyses were conducted on the intent-to-treat (ITT) population with last observation carried forward (LOCF) for missing data using analysis of covariance (ANCOVA) models. The models were run at each post-CAC time point at Visits 3B and 4, with the average of the subjects' post-CAC scores at Visit 2 (Day -14) included as a covariate. Cetirizine was compared to vehicle, and least squares means (LS Means) and the corresponding 95% confidence intervals were provided.

Two-sample t-tests were used as unadjusted sensitivity analyses at each post-CAC time point, as well as non-parametric Wilcoxon rank sum tests. At each post-challenge time point, treatment differences were considered statistically significant for each primary endpoint if they showed significance at a two-sided significance level of $\alpha = 0.05$. Sensitivity or supportive analyses were performed on the ITT population with a multiple imputation (MI) method using Markov Chain

Monte Carlo (MCMC), Baseline Observation Carried Forward (BOCF, missing data at Visits 3B and 4 will be imputed from the corresponding time point at Visit 2) and with Observed Data Only (ODO), as well as the Per Protocol (PP) population with observed data only.

It is noted that the results of the unadjusted two-sample t-tests at each post-CAC time point on the ITT population with LOCF for missing data were reported in the proposed label and presented in the summary of clinical efficacy. These results were similar as the results using ANCOVA on the ITT population with LOCF for missing data and the overall conclusion did not change. The statistical reviewer considered both approaches acceptable; and hence to be consistent with the applicant-proposed label, the results based on two-sample t-test were reported as the primary efficacy results throughout this statistical review.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 11-100-0012

Ninety-one subjects were randomized into the study at Visit 3A, including 46 in the cetirizine group and 45 in the Vehicle group. All of the 91 randomized subjects received their first dose of assigned study medication in-office at Visit 3A, and thus comprise both the ITT population and the Safety population. Two subjects in the ITT population (both in the cetirizine group) did not complete the study because they manifested clinically active signs or symptoms of allergic conjunctivitis at Visit 4.

Table 7: Study 11-100-0012 Subjects' Disposition

	Cetirizine n (%)	Vehicle n (%)	Overall n (%)
Number of Subjects Randomized (ITT and Safety Population)	46 (100%)	45 (100%)	91 (100%)
PP Population^b	44 (95.7%)	45 (100%) ^c	87 (97.8%)
Discontinued the Study Early	2 (4.3%)	0	2 (2.2%)
Reasons for Early Discontinuation			
Lack of efficacy	2 (4.3%)	0	2 (2.2%)

Source: Table 5 of Study 11-100-0012 report.

As presented in the following table, demographic and baseline characteristics were comparable between the treatment groups.

Table 8: Study 11-100-0012 Demographic and Baseline Characteristics (ITT)

Characteristics	Cetirizine (N=46)	Vehicle (N=45)	Total (N=91)
	n (%)	n (%)	n (%)
Gender			
Male	22 (47.8)	17 (37.8)	39 (42.9)
Female	24 (52.2)	28 (62.2)	52 (57.1)

Characteristics	Cetirizine (N=46)	Vehicle (N=45)	Total (N=91)
	n (%)	n (%)	n (%)
Age			
Mean (Std)	36.6 (14.95)	38.1 (14.08)	37.4 (14.47)
Min, Max	14, 73	11, 64	11, 73
Median	35.0	37.0	37.0
Race			
White/Caucasian	30 (65.2)	33 (73.3)	63 (69.2)
Black/African American	9 (19.6)	5 (11.1)	14 (15.4)
American Indian or Alaskan Native	7 (15.2)	7 (15.6)	14 (15.4)
Ethnicity			
Hispanic or Latino	12 (26.1)	13 (28.9)	25 (27.5)
Non-Hispanic or Latino	34 (73.9)	32 (71.1)	66 (72.5)
Iris Color^a			
Brown	48 (52.2)	58 (64.4)	106 (58.2)
Blue	19 (20.7)	10 (11.1)	29 (15.9)
Hazel	20 (21.7)	12 (13.3)	32 (17.6)
Green	5 (5.4)	6 (6.7)	11 (6.0)
Black	0 (0.0)	2 (2.2)	2 (1.1)
Gray	0 (0.0)	2 (2.2)	2 (1.1)

^a Iris Color are based on the total number of eyes randomized in each treatment group
Source: Tables 8 and Table 14.1.2 of Study 11-100-0012 report.

3.2.3.2 Study 12-100-0006

One hundred subjects were randomized into the study at Visit 3A, including 50 in the cetirizine group and 50 in the Vehicle group. All of the 100 randomized subjects received their first dose of assigned study medication in-office at Visit 3A, and thus comprise both the ITT population and the Safety population. Four subjects in the ITT population (one in the cetirizine group and three in the vehicle group) did not complete the study because of various reasons (see table below).

Table 9: Study 12-100-0006 Subjects' Disposition

	Cetirizine n (%)	Vehicle n (%)	Overall n (%)
Number of Subjects Randomized (ITT and Safety Population)	50 (100%)	50 (100%)	100 (100%)
PP Population^b	49 (98.0%)	47 (94.0%) ^c	96 (96.0%)
Discontinued the Study Early	1 (2.0%)	3 (6.0%)	2 (2.0%)
Reasons for Early Discontinuation			
Adverse events	1 (2.0%)	1 (2.0%)	2 (2.0%)
Administrative Reasons	0 (0.0%)	1 (2.0%)	1 (1.0%)
Lack of efficacy	0	1 (2.0%)	1 (1.0%)

Source: Table 5 of Study 12-100-0006 report.

As presented in the following table, demographic and baseline characteristics were comparable between the treatment groups.

Table 10: Study 12-100-0006 Demographic and Baseline Characteristics (ITT)

Characteristics	Cetirizine (N=50)	Vehicle (N=50)	Total (N=100)
	n (%)	n (%)	n (%)
Gender			
Male	13 (26.0)	20 (40.0)	33 (33.0)
Female	37 (74.0)	30 (60.0)	67 (67.0)
Age			
Mean (Std)	39.5 (17.32)	38.1 (14.56)	38.8 (15.93)
Min, Max	11, 74	13, 75	11, 75
Median	38.0	39.5	38.0
Race			
White/Caucasian	44 (88.0)	46 (92.0)	90 (90.0)
Black/African American	3 (6.0)	2 (4.0)	5 (5.0)
Asian	1 (2.0)	2 (4.0)	3 (3.0)
American Indian or Alaskan Native	2 (4.0)	0 (0.0)	2 (2.0)
Ethnicity			
Hispanic or Latino	11 (22.0)	4 (8.0)	15 (15.0)
Non-Hispanic or Latino	39 (78.0)	46 (92.0)	85 (85.0)
Iris Color^a			
Black	2 (2.0)	0 (0.0)	2 (1.0)
Blue	34 (34.0)	36 (36.0)	70 (35.0)
Brown	38 (38.0)	36 (36.0)	74 (37.0)
Hazel	14 (14.0)	14 (14.0)	28 (14.0)
Green	12 (12.0)	14 (14.0)	26 (13.0)

^a Iris Color are based on the total number of eyes randomized in each treatment group
Source: Tables 8 and Table 14.1.2 of Study 12-100-0006 report.

3.2.3.3 Study 13-100-0002

One hundred and one subjects were randomized into the study at Visit 3A, including 51 in the cetirizine group and 50 in the Vehicle group. All of the 101 randomized subjects received their first dose of assigned study medication in-office at Visit 3A, and thus comprise both the ITT population and the Safety population. Fourteen subjects (13.9%) in the ITT population (8 [15.7%] in the cetirizine group and 6 [12.0%] in the vehicle group) did not complete the study because of various reasons (see table below).

Table 11: Study 13-100-0002 Subjects' Disposition

	Cetirizine n (%)	Vehicle n (%)	Overall n (%)
Number of Subjects Randomized (ITT and Safety Population)	51 (100%)	50 (100%)	101 (100%)

PP Population^b	43 (84.3%)	44 (88.0%)	87 (86.1%)
Discontinued the Study Early	8 (15.7%)	6 (12.0%)	14 (13.9%)
Reasons for Early Discontinuation			
Protocol Violations	3 (5.9%)	2 (4.0%)	5 (5.0%)
Administrative Reasons	3 (5.9%)	2 (4.0%)	5 (5.0%)
Lack of efficacy	2 (3.9%)	2 (4.0%)	4 (4.0%)

Source: Table 5 of Study 13-100-0002 report.

As presented in the following table, demographic and baseline characteristics were comparable between the treatment groups.

Table 12: Study 13-100-0002 Demographic and Baseline Characteristics (ITT)

Characteristics	Cetirizine (N=51)	Vehicle (N=50)	Total (N=101)
	n (%)	n (%)	n (%)
Gender			
Male	12 (23.5)	20 (40.0)	32 (31.7)
Female	39 (76.5)	30 (60.0)	69 (68.3)
Age			
Mean (Std)	40.6 (12.80)	39.2 (10.84)	39.9 (11.84)
Min, Max	18, 68	18, 71	18, 71
Median	41.0	39.5	39.9
Race			
White/Caucasian	41 (80.4)	31 (62.0)	72 (71.3)
Black/African American	10 (19.6)	17 (34.0)	27 (26.7)
Asian	0 (0.0)	1 (2.0)	1 (1.0)
American Indian or Alaskan Native			
Ethnicity			
Hispanic or Latino	1 (2.0)	0 (0.0)	1 (1.0)
Non-Hispanic or Latino	50 (98.0)	50 (100.0)	100 (99.0)
Iris Color^a			
Black	2 (2.0)	4 (4.0)	6 (3.0)
Blue	36 (35.3)	18 (18.0)	54 (26.7)
Brown	38 (37.3)	60 (60.0)	98 (48.5)
Hazel	12 (11.8)	6 (6.0)	18 (8.9)
Green	14 (13.7)	12 (12.0)	26 (12.9)

^a Iris Color are based on the total number of eyes randomized in each treatment group

Source: Tables 8 and Table 14.1.2 of Study 13-100-0002 report.

3.2.4 Results and Conclusions

3.2.4.1 Ocular Itching Scores

For the primary efficacy endpoint of ocular itching score, all three studies (11-100-0012, 13-100-0002, and 12-100-0006) demonstrated statistical superiority of cetirizine to vehicle at Visit 3B (duration-of-action) and Visit 4 (onset-of-action).

For Study 11-100-0012,

- On Visit 3B (16 hours duration-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.71, and 2.34 respectively; the treatment difference was -0.64 with a 95% CI of (-0.95, -0.33); at 5-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.88, and 2.50 respectively; the treatment difference was -0.62 with a 95% CI of (-0.95, -0.29); at 7-minute post-CAC, the mean itching score for cetirizine was 1.76, and 2.22 for the vehicle group; the treatment difference was -0.46 with a 95% CI of (-0.84, -0.08).
- On Visit 4 (onset-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 0.71, and 2.18 respectively; the treatment difference was -1.47 with a 95% CI of (-1.82, -1.12); at 5-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.01, and 2.31 respectively; the treatment difference was -1.31 with a 95% CI of (-1.66, -0.95); at 7-minute post-CAC, the mean itching score for cetirizine was 1.00, and 2.10 for the vehicle group; the treatment difference was -1.10 with a 95% CI of (-1.48, -0.72).

For Study 12-100-0006,

- On Visit 3B (8 hours duration-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.76, and 2.69 respectively; the treatment difference was -0.93 with a 95% CI of (-1.26, -0.61); at 5-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.85, and 2.74 respectively; the treatment difference was -0.89 with a 95% CI of (-1.24, -0.54); at 7-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.54, and 2.53 respectively; the treatment difference was -0.99 with a 95% CI of (-1.40, -0.59).
- On Visit 4 (onset-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.00, and 2.38 respectively; the treatment difference was -1.38 with a 95% CI of (-1.72, -1.05); at 5-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.18, and 2.43 respectively; the treatment difference was -1.25 with a 95% CI of (-1.58, -0.91); at 7-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.11, and 2.11 respectively; the treatment difference was -1.00 with a 95% CI of (-1.35, -0.65).

For Study 13-100-0002,

- On Visit 3B (8 hours duration-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.94, and 2.86 respectively; the treatment difference was -0.92 with a 95% CI of (-1.25, -0.58); at 5-minute post-CAC, the mean

itching scores for cetirizine and vehicle groups were 2.03, and 2.94 respectively; the treatment difference was -0.90 with a 95% CI of (-1.23, -0.57); at 7-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.82, and 2.66 respectively; the treatment difference was -0.84 with a 95% CI of (-1.21, -0.48).

- On Visit 4 (onset-of-action): At 3-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.00, and 2.38 respectively; the treatment difference was -1.38 with a 95% CI of (-1.72, -1.05); at 5-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.18, and 2.43 respectively; the treatment difference was -1.25 with a 95% CI of (-1.58, -0.91); at 7-minute post-CAC, the mean itching scores for cetirizine and vehicle groups were 1.11, and 2.11 respectively; the treatment difference was -1.00 with a 95% CI of (-1.35, -0.65).

Table 13: Ocular Itching Scores by Treatment Group and Treatment Difference (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹		
				Time Post-CAC			Time Post-CAC		
				3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	Cetirizine	46/44	15 min	0.71	1.01	1.00	-1.47	-1.31	-1.10
	Vehicle	45/45		2.18	2.31	2.10	(-1.82, -1.12)	(-1.66, -0.95)	(-1.48, -0.72)
	Cetirizine	46/44	16 hours	1.71	1.88	1.76	-0.64	-0.62	-0.46
	Vehicle	45/45		2.34	2.50	2.22	(-0.95, -0.33)	(-0.95, -0.29)	(-0.84, -0.08)
12-100-0006	Cetirizine	50/49	15 min	1.00	1.18	1.11	-1.38	-1.25	-1.00
	Vehicle	50/47		2.38	2.43	2.11	(-1.72, -1.05)	(-1.58, -0.91)	(-1.35, -0.65)
	Cetirizine	50/49	8 hours	1.76	1.85	1.54	-0.93	-0.89	-0.99
	Vehicle	50/47		2.69	2.74	2.53	(-1.26, -0.61)	(-1.24, -0.54)	(-1.40, -0.59)
13-100-0002	Cetirizine	51/43	15 min	1.01	1.17	1.15	-1.53	-1.34	-1.07
	Vehicle	50/44		2.54	2.51	2.23	(-1.92, -1.15)	(-1.71, -0.97)	(-1.46, -0.69)
	Cetirizine	51/43	8 hours	1.94	2.03	1.82	-0.92	-0.90	-0.84
	Vehicle	50/44		2.86	2.94	2.66	(-1.25, -0.58)	(-1.23, -0.57)	(-1.21, -0.48)

* Post study drug instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Source: Table 5 of Summary of Clinical Efficacy.

In study 11-100-0012, two subjects (2.2% [2/91], both in cetirizine group) did not complete the study and had missing values. In study 12-100-0006, four subjects (4% [4/100]), including one (2%, [1/50]) in cetirizine group and three (6%, [3/50]) in vehicle group, did not complete the study and had missing values. For these two studies, the percentages of subjects with missing values were less than 5%; therefore, the statistical reviewer considered the impact of the missing values to the efficacy conclusion to be minimal.

In study 13-100-0002, a total of 14 subjects (13.9%) discontinued the study early and therefore had missing values; 8 subjects (15.7% [8/51]) in cetirizine group and 6 subjects (12.0% [6/50]) in vehicle group. Four subjects (2 in cetirizine group and 2 in vehicle group) discontinued due to lack of efficacy; five subjects (3 in cetirizine group and 2 in vehicle group) discontinued due to protocol violations; and five subjects (3 in cetirizine group and 2 in vehicle group) discontinued due to administrative reasons.

Table 14: Summary of Patients Discontinuation (Studies 11-100-0012, 12-100-0006, and 13-100-0002)

	Cetirizine n (%)	Vehicle n (%)	Overall n (%)
Study 11-100-0012	N=46	N=45	N=91
Discontinued the Study Early	2 (4.3%)	0	2 (2.2%)
Reasons for Early Discontinuation			
Lack of efficacy	2 (4.3%)	0	2 (2.2%)
Study 12-100-0006	N=50	N=50	N=100
Discontinued the Study Early	1 (2.0%)	3 (6.0%)	4 (4.0%)
Reasons for Early Discontinuation			
Adverse events	1 (2.0%)	1 (2.0%)	2 (2.0%)
Administrative Reasons	0 (0.0%)	1 (2.0%)	1 (1.0%)
Lack of efficacy	0	1 (2.0%)	1 (1.0%)
Study 13-100-0002	N=51	N=50	N=101
Discontinued the Study Early	8 (15.7%)	6 (12.0%)	14 (13.9%)
Reasons for Early Discontinuation			
Protocol Violations	3 (5.9%)	2 (4.0%)	5 (5.0%)
Administrative Reasons	3 (5.9%)	2 (4.0%)	5 (5.0%)
Lack of efficacy	2 (3.9%)	2 (4.0%)	4 (4.0%)

Source: Table 5 of Study 11-100-0012 report; Table 5 of Study 12-100-0006 report; and Table 5 of Study 13-100-0002 report.

For subjects discontinued due to lack of efficacy, LOCF for imputing missing values might be questionable. As part of the sensitivity analyses, the applicant analyzed the ocular itching scores with baseline observation carried forward (BOCF) for observations with missing values. For BOCF, missing data at Visits 3B and 4 were imputed from the corresponding time point at Visit 2, i.e., a missing 5-minute observation at Visit 4 will be imputed from the 5-minute observation at Visit 2, etc.). The results (Table 15) were consistent with the efficacy analyses results presented above.

Table 15: Ocular Itching Scores by Treatment Group and Treatment Difference (ITT, BOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹		
				Time Post-CAC			Time Post-CAC		
				3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	Cetirizine	46/44	15	0.77	1.08	1.08	-1.42	-1.23	-1.02
	Vehicle	45/45	min	2.18	2.31	2.10	(-1.77, -1.06)	(-1.60, -0.86)	(-1.41, -0.64)
	Cetirizine	46/44	16	1.70	1.89	1.77	-0.64	-0.61	-0.46
	Vehicle	45/45	hours	2.34	2.50	2.22	(-0.98, -0.31)	(-0.94, -0.29)	(-0.83, -0.08)
12-100-0006	Cetirizine	50/49	15	1.04	1.22	1.14	-1.36	-1.23	-0.98
	Vehicle	50/47	min	2.40	2.44	2.12	(-1.69, -1.03)	(-1.55, -0.90)	(-1.33, -0.63)
	Cetirizine	50/49	8	1.78	1.87	1.56	-0.91	-0.87	-0.97
	Vehicle	50/47	hours	2.69	2.74	2.53	(-1.23, -0.59)	(-1.22, -0.51)	(-1.37, -0.57)
13-100-0002	Cetirizine	51	15	1.15	1.33	1.34	-1.43	-1.26	-0.97
	Vehicle	50	min	2.59	2.59	2.31	(-1.84, -1.02)	(-1.66, -0.85)	(-1.41, -0.54)
	Cetirizine	51	8	1.94	2.03	1.82	-0.90	-0.88	-0.84
	Vehicle	50	hours	2.84	2.92	2.66	(-1.23, -0.57)	(-1.21, -0.55)	(-1.21, -0.48)

* Post study drug instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Sensitivity analyses were performed on the ITT population with a multiple imputation (MI) method using Markov Chain Monte Carlo (MCMC), and with observed data only (ODO), as well as the Per Protocol (PP) population with observed data only. The results of these sensitivity analyses were supportive of the efficacy analyses results presented above.

According to the protocol-defined clinical criteria for efficacy, to demonstrate efficacy at a visit, cetirizine needed to show clinical superiority over vehicle by a mean difference of at least 0.5 units of a 5 point scale for all post-CAC time points, and by at least 1 unit for the majority of the post-CAC time points (i.e. 2 out of 3) for ocular itching. For the three studies, at Visit 4, mean treatment differences were greater than 1 unit for all time points, and all treatment differences were statistically significant, and thus the clinical criteria for efficacy were met at Visit 4 for ocular itching. However, at Visit 3B, post-CAC mean treatment differences were less than 1 unit for all of the three time points in Studies 11-100-0012, 12-100-0006 and 13-100-0002; therefore, the clinical criteria for efficacy were not met for all three studies at Visit 3B.

The statistical reviewer analyzed the percentage of subjects with 1 unit improvement from baseline in ocular itching scores in each study. For this analysis, missing data at Visits 3B and 4 were imputed from the corresponding time point at Visit 2, i.e., a missing 5-minute observation at Visit 4 will be imputed from the 5-minute observation at Visit 2, etc. (BOCF). Other than the 7-minute post-CAC at Visit 3B (16-hour duration-of-action) in Study 11-100-0012, the results of this responders' analysis were statistically significant at all other time points in both Visit 3B and Visit 4 for the three studies (Table 16).

Table 16: Percentage of Subjects with 1 Unit Improvement from Baseline in Ocular Itching Scores at Each Post-CAC Time Point (ITT, BOCF)

Study	Treatment	CAC*	n/N (Percentage)			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	Cetirizine	15 min	40/46 (87.0)	37/46 (80.4)	35/46 (76.1)	53.6% (36.8%, 70.5%)	47.1% (29.2%, 65.0%)	31.6% (12.6%, 50.7%)
	Vehicle		15/45 (33.3)	15/45 (33.3)	20/45 (44.4)			
	Cetirizine	16 hours	21/46 (45.7)	20/46 (43.5)	20/46 (43.5)	19.0% (0.0%, 38.3%)	25.7% (7.5%, 43.9%)	14.6% (-4.9%, 34.1%)
	Vehicle		12/45 (26.7)	8/45 (17.8)	13/45 (28.9)			
12-100-0006	Cetirizine	15 min	42/50 (84.0)	43/50 (86.0)	43/50 (86.0)	62.0% (46.7%, 77.3%)	58.0% (42.3%, 73.7%)	48.0% (31.5%, 64.5%)
	Vehicle		11/50 (22.0)	14/50 (28.0)	19/50 (38.0)			
	Cetirizine	8 hours	25/50 (50.0)	29/50 (58.0)	30/50 (60.0)	38.0% (21.5%, 54.5%)	36.0% (18.1%, 53.9%)	34% (15.8%, 52.2%)
	Vehicle		6/50 (12.0)	11/50 (22.0)	13/50 (26.0)			
13-100-0002	Cetirizine	15 min	39/51 (76.5)	39/51 (76.5)	40/51 (78.4)	44.5% (27.1%, 61.9%)	40.5% (22.8%, 58.2%)	32.4% (50.3%, 14.6%)
	Vehicle		16/50 (32.0)	18/50 (36.00)	23/50 (46.0)			

	Cetirizine	8	26/51 (51.0)	30/51 (58.8)	35/51 (68.6)	31.0% (13.3%, 48.6%)	32.8% (14.7%, 51.0%)	42.6% (25.0%, 60.2%)
	Vehicle	hours	10/50 (20.0)	13/50 (26.0)	13/50 (26.0)			

* Post study drug instillation.

¹ 95% CI was based on normal approximation to binomial data.

Source: Statistical Reviewer's Analyses.

From statistical perspective, the treatment differences at all the time points were statistically significant; and the point estimates of the treatment differences and their corresponding 95% CI were consistent across different studies; in addition, the responders' analysis was also supportive of the primary efficacy results. Therefore, the statistical reviewer considered that the collective evidence of the three studies demonstrated statistical superiority of cetirizine to vehicle at Visit 3B (duration-of-action) and Visit 4 (onset-of-action) in terms of ocular itching score. Whether the results are clinically relevant is beyond the scope of this statistical review.

3.2.4.2 Conjunctival Redness Scores

For the co-primary efficacy endpoint of conjunctival redness scores, Studies 11-100-0012 and 12-100-0006 failed to demonstrate statistical superiority of cetirizine to vehicle at Visit 3B (duration-of-action) and at Visit 4 (onset-of-action). Studies 13-100-0002 failed to demonstrate statistical superiority of cetirizine to vehicle at Visit 4 (onset-of-action); at the 8-hour duration-of-action evaluation, conjunctival redness scores were significantly lower in the cetirizine group compared to vehicle group; however, results did not differ by more than 0.5 unit.

Table 17: Conjunctival Redness Scores by Treatment Group and Treatment Difference (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹		
				Time Post-CAC			Time Post-CAC		
				7 min	15 min	20 min	7 min	15 min	20 min
11-100-0012	Cetirizine	46/44	15 min	2.02	2.23	2.28	-0.03 (-0.34, 0.27)	0.09 (-0.20, 0.39)	0.10 (-0.19, 0.40)
	Vehicle	45/45		2.05	2.13	2.18			
	Cetirizine	46/44	16 hours	1.72	1.96	1.92	-0.22 (-0.55, 0.11)	-0.06 (-0.39, 0.27)	-0.06 (-0.38, 0.26)
	Vehicle	45/45		1.94	2.02	1.98			
12-100-0006	Cetirizine	50/49	15 min	1.66	1.93	1.95	-0.33 (-0.53, -0.06)	-0.03 (-0.26, 0.19)	-0.01 (-0.26, 0.23)
	Vehicle	50/47		1.98	2.09	2.09			
	Cetirizine	50/49	8 hours	1.97	2.30	2.30	-0.30 (-0.53, -0.06)	-0.03 (-0.26, 0.19)	-0.01 (-0.26, 0.23)
	Vehicle	50/47		2.27	2.34	2.32			
13-100-0002	Cetirizine	51/43	15 min	1.92	2.19	2.15	-0.46 (-0.73, -0.19)	-0.18 (-0.43, 0.07)	-0.25 (-0.51, 0.00)
	Vehicle	50/44		2.38	2.37	2.41			
	Cetirizine	51/43	8 hours	1.97	2.13	2.09	-0.42 (-0.68, -0.16)	-0.24 (-0.49, 0.00)	-0.31 (-0.58, -0.05)
	Vehicle	50/44		2.39	2.38	2.40			

* Post study drug instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Source: Table 6 of Summary of Clinical Efficacy.

In addition, the statistical reviewer analyzed the percentage of subjects with 0.5 unit improvement from baseline in conjunctival redness scores in each study. For this analyses,

missing data at Visits 3B and 4 were imputed from the corresponding time point at Visit 2, i.e., a missing 5-minute observation at Visit 4 will be imputed from the 5-minute observation at Visit 2, etc. (BOCF). Other than the 7-minute post-CAC at Visit 4 (onset-of-action) in Study 12-100-0006, none of the results of this responders' analysis were statistically significant at all other time points in both Visit 3B and Visit 4 for the three studies (Table 18).

Table 18: Percentage of Subjects with 0.5 Unit Improvement from Baseline in Conjunctival Redness Scores at Each Post-CAC Time Point (ITT, BOCF)

Study	Treatment	CAC*	n/N (Percentage)			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			7 min	15 min	20 min	7 min	15 min	20 min
11-100-0012	Cetirizine	15 min	13/46 (28.3)	10/46 (21.7)	6/46 (13.0)	1.6%	-7.2%	-13.6%
	Vehicle		12/45 (26.7)	13/45 (28.9)	12/45 (26.7)	(-16.7%, 19.9%)	(-25.0%, 10.7%)	(-29.8%, 2.6%)
	Cetirizine	16 hours	25/46 (54.4)	21/46 (45.7)	22/46 (47.8)	12.1%	1.2%	5.6%
	Vehicle		19/45 (42.2)	20/45 (44.4)	19/45 (42.2)	(-8.3%, 32.5%)	(-19.2%, 21.7%)	(-14.8%, 26.0%)
12-100-0006	Cetirizine	15 min	40/50 (80.0)	33/50 (66.0)	29/50 (58.0)	20.0%	12.0%	4.0%
	Vehicle		30/50 (60.0)	27/50 (54.0)	27/50 (54.0)	(2.5%, 37.5%)	(-7.0%, 31.1%)	(-15.4%, 23.4%)
	Cetirizine	8 hours	25/50 (50.0)	20/50 (40.0)	20/50 (40.0)	12.0%	-6.0%	-2.0%
	Vehicle		19/50 (38.0)	23/50 (46.0)	21/50 (42.0)	(-7.3%, 31.3%)	(-25.4%, 13.4%)	(-21.3%, 17.3%)
13-100-0002	Cetirizine	15 min	27/51 (52.9)	19/51 (37.3)	20/51 (39.2)	10.9%	-0.1%	-0.1%
	Vehicle		21/50 (42.0)	19/50 (38.0)	20/50 (40.0)	(-8.4%, 30.3%)	(-19.6%, 18.2%)	(19.9%, 18.3%)
	Cetirizine	8 hours	30/51 (58.8)	28/51 (54.9)	28/51 (54.9)	10.8%	4.9%	10.9%
	Vehicle		24/50 (48.0)	25/50 (50.0)	22/50 (44.0)	(-8.5%, 30.2%)	(-14.6%, 24.4%)	(-8.5%, 30.3%)

* Post study drug instillation.

¹ 95% CI was based on normal approximation to binomial data.

Source: Statistical Reviewer's Analyses.

Therefore, the statistical reviewer concluded that there was not enough evidence to support the superiority of cetirizine to vehicle in terms of conjunctival redness scores.

3.2.4.3 Overall Conclusion

All three studies defined ocular itching scores and conjunctival redness scores as co-primary efficacy endpoints and tested each endpoint at a significant level of 0.05. Based on the statistical reviewer's understanding of co-primary efficacy endpoint, in order for a study to claim being successful, both endpoints have to demonstrate statistical significance. With the three studies failing to demonstrate a statistically significant treatment effect in conjunctival redness scores, the reviewer further examined the statistical evidence of cetirizine treatment in ocular itching to address the resultant multiplicity issue.

As shown in Table 19, the p-values were less than 0.025 for all evaluations of onset and duration-of-action. Had the applicant split the 0.05 alpha level between the two co-primary efficacy endpoints (0.025 alpha level for each of the primary efficacy endpoints), all three studies would still have had demonstrated statistical superiority of cetirizine to vehicle at each post-CAC time point (3-, 5-, and 7-minute) for each efficacy evaluation visit (Visits 3B and Visit 4) for ocular itching scores. Therefore, the statistical reviewer considered that there were substantial statistical evidence to support the superiority of cetirizine to vehicle at Visit 3B (duration-of-action) and Visit 4 (onset-of-action) in terms of ocular itching score.

Table 19: P-values for Ocular Itching Scores by Time Point and Study Visit (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score (SD)			p-value for Treatment Difference ¹ Time Post-CAC		
				Time Post-CAC			3 min	5 min	7 min
				3 min	5 min	7 min			
11-100-0012	Cetirizine	46/44	15 min	0.71 (0.64)	1.01 (0.69)	1.00 (0.78)	<0.0001	<0.0001	<0.0001
	Vehicle	45/45		2.18 (0.98)	2.31 (0.98)	2.10 (1.00)			
	Cetirizine	46/44	16 hours	1.71 (0.87)	1.88 (0.91)	1.76 (0.94)	0.0003	0.0004	0.0184
	Vehicle	45/45		2.34 (0.72)	2.50 (0.64)	2.22 (0.88)			
12-100-0006	Cetirizine	50/49	15 min	1.00 (0.91)	1.18 (0.93)	1.11 (0.86)	<0.0001	<0.0001	<0.0001
	Vehicle	50/47		2.38 (0.72)	2.43 (0.69)	2.11 (0.87)			
	Cetirizine	50/49	8 hours	1.76 (0.94)	1.85 (0.94)	1.54 (0.97)	<0.0001	<0.0001	<0.0001
	Vehicle	50/47		2.69 (0.66)	2.74 (0.82)	2.53 (1.06)			
13-100-0002	Cetirizine	51/43	15 min	1.01 (1.00)	1.17 (1.00)	1.15 (1.00)	<0.0001	<0.0001	<0.0001
	Vehicle	50/44		2.54 (0.94)	2.51 (0.88)	2.23 (0.96)			
	Cetirizine	51/43	8 hours	1.94 (0.93)	2.03 (0.95)	1.82 (1.03)	<0.0001	<0.0001	<0.0001
	Vehicle	50/44		2.86 (0.75)	2.94 (0.71)	2.66 (0.1)			

* Post study drug instillation.

¹ P-value was calculated using a two-sample t-test comparing active treatment to vehicle at each individual time point.

Source: Table 9 of Study 11-100-0012 Report, Table 9 of Study 12-100-0006 Report, and Tables 9 and 10 of Study 13-100-0002 Report.

3.3 Evaluation of Safety

For Study 11-100-0012, all 91 subjects who were exposed to the study treatment were included in the safety analysis set. For Study 12-100-0006, the 100 subjects who were exposed to the study treatment were included in the safety analysis set. For Study 13-100-0002, the 101 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 the three studies. Overall, cetirizine had similar adverse events rates as vehicle-treated groups. Please see the review of the medical reviewer for details of the safety evaluation.

Table 20: Summary of Treatment-Emergent Adverse Events (Studies 11-100-0012, 12-100-0006, and 13-100-0002, Safety Analysis Set)

	11-100-0012		12-100-0006		13-100-0002	
	Cetirizine (N=46)	Vehicle (N=45)	Cetirizine (N=50)	Vehicle (N=50)	Cetirizine (N=51)	Vehicle (N=50)
Ocular Treatment-Emergent Adverse Events						
Eye Disorders	1 (2.2%)	2 (4.4%)	1 (2.0%)	3 (6.0%)	1 (2.0%)	1 (2.0%)

Conjunctival haemorrhage	1 (2.2%)	0 (0.0%)	NA	NA	NA	NA
Visual acuity reduced	0 (0.0%)	1 (2.2%)	0 (0.0%)	2 (4.0%)	1 (2.0%)	1 (2.0%)
Eye pain	NA	NA	1 (2.0%)	0 (0.0%)	NA	NA
Punctate Keratitis	NA	NA	0 (0.0%)	1 (2.0%)	NA	NA
Infections and Infestations	0 (0.0%)	1 (2.2%)	NA	NA	NA	NA
Hordeolum	0 (0.0%)	1 (2.2%)	NA	NA	NA	NA
Non-Ocular Treatment-Emergent Adverse Events						
	0 (0.0%)	3 (6.6%)	2 (4.0%)	2 (4.0%)	2 (3.9%)	3 (6.0%)
Infections and Infestations	0 (0.0%)	1 (2.2%)	0 (0.0%)	2 (4.0%)	NA	NA
Nasopharyngitis	0 (0.0%)	1 (2.2%)	NA	NA	NA	NA
Lower Respiratory Tract Infection	NA	NA	0 (0.0%)	1 (2.0%)	NA	NA
Sinusitis	NA	NA	0 (0.0%)	1 (2.0%)	NA	NA
Respiratory, Thoracic and Mediastinal Disorders	0 (0.0%)	1 (2.2%)	2 (4.0%)	0 (0.0%)	0 (0.0%)	2 (4.0%)
Oropharyngeal Pain	0 (0.0%)	1 (2.2%)	NA	NA	NA	NA
Cough	NA	NA	1 (2.0%)	0 (0.0%)	NA	NA
Pharyngeal Oedema	NA	NA	1 (2.0%)	0 (0.0%)	NA	NA
Epistaxis	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)
Rhinitis Allergic	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)
Musculoskeletal and Connective Tissue Disorders	0 (0.0%)	1 (2.2%)	1 (2.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Myalgia	0 (0.0%)	1 (2.2%)	1 (2.0%)	0 (0.0%)	NA	NA
Rheumatoid Arthritis	NA	NA	1 (2.0%)	0 (0.0%)	NA	NA
Neck Pain	NA	NA	NA	NA	1 (2.0%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	0 (0.0%)	1 (2.2%)	NA	NA	1 (2.0%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (2.2%)	NA	NA	NA	NA
Dermatitis Contact	NA	NA	NA	NA	1 (2.0%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)
Pruritus	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)
Vascular Disorders	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)
Pruritus	NA	NA	NA	NA	0 (0.0%)	1 (2.0%)

Subjects experiencing more than one TEAE within a given system organ class (SOC) or preferred term (PT) are counted once within that SOC or PT in the Subjects column.

Source: Tables 22 and 23 of Study 11-100-0012 Report; Tables 24 and 25 of Study 12-100-0006 Report; Tables 36 and 37 of Study 13-100-0002 Report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Subgroup analyses based on gender, race, and age were performed. In general, there were no marked differences in the efficacy results among the various subpopulations for the three studies.

Table 21: Study 11-100-0012 Ocular Itching Scores Subgroup Analyses (ITT, LOCF)

Visit 3B (16-Hour Duration-of-action)							
Subgroup	Treatment	Mean Score			Treatment Difference (95% CI) ¹		
		Time Post-CAC			Time Post-CAC		
		3 min	5 min	7 min	3 min	5 min	7 min

Gender	Female	Cetirizine	1.71	1.88	1.69	-0.60	-0.55	-0.46
		Vehicle	2.31	2.43	2.15	(-1.06, -0.14)	(-0.97, -0.14)	(-0.95, 0.03)
	Male	Cetirizine	1.70	1.89	1.85	-0.69	-0.72	-0.49
		Vehicle	2.40	2.62	2.34	(-1.23, -0.16)	(-1.29, -0.16)	(-1.14, 0.15)
Age	<65	Cetirizine	1.70	1.88	1.77	-0.65	-0.63	-0.45
		Vehicle	2.34	2.50	2.22	(-0.99, -0.30)	(-0.96, -0.29)	(-0.84, -0.07)
	≥65	Cetirizine	1.83	2.00	1.67	n/a	n/a	n/a
		Vehicle	n/a	n/a	n/a			
Race	White	Cetirizine	1.71	1.93	1.81	-0.60	-0.54	-0.39
		Vehicle	2.31	2.48	2.20	(-1.03, -0.17)	(-0.97, -0.12)	(-0.89, 0.09)
	Non-White	Cetirizine	1.70	1.78	1.67	-0.74	-0.78	-0.63
		Vehicle	2.44	2.56	2.29	(-1.31, -0.17)	(-1.31, -0.25)	(-1.30, 0.05)
Visit 4 (Onset-of-action)								
Subgroup		Treatment	Mean Score			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
Gender	Female	Cetirizine	0.65	0.96	0.90	-1.40	-1.21	-0.98
		Vehicle	2.04	2.17	1.88	(-1.84, -0.96)	(-1.67, -0.75)	(-1.48, -0.48)
	Male	Cetirizine	0.79	1.06	1.13	-1.62	-1.48	-1.35
		Vehicle	2.41	2.54	2.47	(-2.21, -1.03)	(-2.08, -0.89)	(-1.92, 0.77)
Age	<65	Cetirizine	0.71	0.99	1.01	-1.48	-1.32	-1.09
		Vehicle	2.18	2.31	2.10	(-1.83, -1.12)	(-1.68, -0.95)	(-1.48, -0.70)
	≥65	Cetirizine	0.75	1.25	0.75	n/a ²	n/a ²	n/a ²
		Vehicle	n/a ²	n/a ²	n/a ²			
Race	White	Cetirizine	0.71	1.07	1.07	-1.48	-1.25	-1.04
		Vehicle	2.19	2.33	2.11	(-1.89, -1.06)	(-1.67, -0.83)	(-1.49, -0.59)
	Non-White	Cetirizine	0.70	0.89	0.88	-1.46	-1.38	-1.19
		Vehicle	2.17	2.27	2.06	(-2.19, -0.74)	(-2.21, -0.56)	(-1.95, -0.42)

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

² There was no subject in Vehicle group who was ≥65 years old.

Source: Statistical reviewer's analyses

Table 22: Study 12-100-0006 Ocular Itching Scores Subgroup Analyses (ITT, LOCF)

Visit 3B (8-Hour Duration-of-action)								
Subgroup		Treatment	Mean Score			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
Gender	Female	Cetirizine	1.96	2.03	1.66	-0.88	-0.76	-0.92
		Vehicle	2.83	2.79	2.58	(-1.27, -0.48)	(-1.19, -0.32)	(-1.42, -0.41)
	Male	Cetirizine	1.19	1.33	1.19	-1.28	-1.32	-1.27
		Vehicle	2.48	2.65	2.46	(-1.80, -0.77)	(-1.92, -0.73)	(-2.00, -0.54)
Age	<65	Cetirizine	1.74	1.83	1.49	-0.95	-0.89	-1.03
		Vehicle	2.70	2.72	2.52	(-1.29, -0.62)	(-1.26, -0.53)	(-1.45, -0.62)
	≥65	Cetirizine	2.00	2.25	2.63	-0.50	-0.75	-0.13
		Vehicle	2.50	3.00	2.75	(-4.38, 3.38)	(-3.79, 2.29)	(-3.02, 2.77)
Race	White	Cetirizine	1.74	1.80	1.48	-0.98	-0.96	-1.08
		Vehicle	2.72	2.77	2.55	(-1.32, -0.65)	(-1.34, -0.59)	(-1.51, -0.64)
	Non-White	Cetirizine	1.88	2.17	1.96	-0.44	-0.21	-0.29
		Vehicle	2.31	2.38	2.25	(-1.87, 0.99)	(-1.51, 1.10)	(-1.50, 0.92)

Visit 4 (Onset-of-action)								
Subgroup		Treatment	Mean Score			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
Gender	Female	Cetirizine	1.06	1.26	1.17	-1.32	-1.08	-0.86
		Vehicle	2.38	2.34	2.04	(-1.77, -0.88)	(-1.51, -0.66)	(-1.30, -0.43)
	Male	Cetirizine	0.83	0.96	0.92	-1.55	-1.59	-1.29
		Vehicle	2.38	2.55	2.21	(-2.08, -1.03)	(-2.16, -1.02)	(-1.94, -0.64)
Age	<65	Cetirizine	0.99	1.15	1.10	-1.40	-1.29	-1.01
		Vehicle	2.39	2.43	2.11	(-1.74, -1.06)	(-1.63, -0.95)	(-1.37, -0.65)
	≥65	Cetirizine	1.13	1.88	1.25	-0.88	-0.13	-0.75
		Vehicle	2.00	2.00	2.00	NE ²	NE ²	NE ²
Race	White	Cetirizine	0.92	1.09	1.01	-1.50	-1.35	-1.13
		Vehicle	2.42	2.44	2.14	(-1.84, -1.16)	(-1.69, -1.00)	(-1.50, -0.77)
	Non-White	Cetirizine	1.58	1.83	1.83	-0.42	-0.48	0.08
		Vehicle	2.00	2.31	1.75	(-1.77, 0.93)	(-1.81, 0.85)	(-1.15, 1.31)

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

² There was only one subject in Vehicle group who was ≥65 years old; therefore the 95% CI was not estimable (NE).

Source: Statistical reviewer's analyses.

Table 23: Study 13-100-0002 Ocular Itching Scores Subgroup Analyses (ITT, LOCF)

Visit 3B (8-Hour Duration-of-action)								
Subgroup		Treatment	Mean Score			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
Gender	Female	Cetirizine	1.96	2.04	1.80	-0.92	-0.91	-0.92
		Vehicle	2.88	2.96	2.73	(-1.35, -0.49)	(-1.33, -0.50)	(-1.40, -0.45)
	Male	Cetirizine	1.85	2.00	1.88	-0.96	-0.90	-0.69
		Vehicle	2.81	2.90	2.56	(-1.53, -0.38)	(-1.51, -0.28)	(-1.30, -0.08)
Age	<65	Cetirizine	1.95	2.06	1.84	-0.91	-0.87	-0.81
		Vehicle	2.86	2.93	2.66	(-1.25, -0.57)	(-1.21, -0.54)	(-1.19, -0.44)
	≥65	Cetirizine	1.50	1.38	1.25	-1.13	-1.63	-1.50
		Vehicle	2.63	3.00	2.75	(-5.72, 3.47)	(-6.92, 3.67)	(-6.98, 3.98)
Race	White	Cetirizine	1.90	1.95	1.77	-0.93	-0.87	-0.80
		Vehicle	2.83	2.82	2.57	(-1.35, -0.52)	(-1.29, -0.45)	(-1.26, -0.34)
	Non-White	Cetirizine	2.10	2.38	2.00	-0.79	-0.74	-0.80
		Vehicle	2.89	3.12	2.80	(-1.43, -0.16)	(-1.29, -0.20)	(-1.45, -0.15)
Visit 4 (Onset-of-action)								
Subgroup		Treatment	Mean Score			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
Gender	Female	Cetirizine	1.04	1.21	1.19	-1.50	-1.22	-0.90
		Vehicle	2.54	2.43	2.09	(-2.01, -1.00)	(-1.71, -0.74)	(-1.41, -0.38)
	Male	Cetirizine	0.92	1.04	1.02	-1.62	-1.58	-1.40
		Vehicle	2.54	2.63	2.43	(-2.25, -1.00)	(-2.19, -0.97)	(-1.98, -0.83)
Age	<65	Cetirizine	1.00	1.17	1.15	-1.56	-1.35	-1.07
		Vehicle	2.56	2.52	2.21	(-1.95, -1.17)	(-1.73, -0.98)	(-1.46, -0.67)
	≥65	Cetirizine	1.25	1.25	1.25	-0.88	-1.00	-1.25

		Vehicle	2.13	2.25	2.50	(-6.89, 5.14)	(-7.27, -5.27)	(-7.05, 4.55)
Race	White	Cetirizine	1.01	1.16	1.17	-1.59	-1.39	-1.00
		Vehicle	2.60	2.56	2.17	(-2.03, -1.15)	(-1.83, -0.96)	(-1.44, -0.55)
	Non-White	Cetirizine	1.03	1.20	1.08	-1.42	-1.23	-1.24
		Vehicle	2.45	2.43	2.32	(-2.32, -0.53)	(-2.07, -0.40)	(-2.13, -0.35)

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Source: Statistical reviewer's analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the three pivotal studies submitted.

All three studies defined ocular itching scores and conjunctival redness scores as co-primary efficacy endpoints. Based on general understanding of co-primary efficacy endpoints, in order for a study to claim being successful, both endpoints have to demonstrate statistical significance. With the three studies failing to demonstrate a statistically significant treatment effect in conjunctival redness scores, the reviewer further examined the statistical evidence of cetirizine treatment in ocular itching to address the resultant multiplicity issue.

As shown in Table 24, the p-values were less than 0.025 for all onset and duration-of-action evaluations. Had the applicant split the 0.05 alpha level between the two co-primary efficacy endpoints (0.025 alpha level for each of the primary efficacy endpoints), all three studies would still have had demonstrated statistical superiority of cetirizine to vehicle at each post-CAC time point (3-, 5-, and 7-minute) for each efficacy evaluation visit (Visits 3B and Visit 4) for ocular itching scores. Therefore, the statistical reviewer considered that there were substantial statistical evidence to support the superiority of cetirizine to vehicle at Visit 3B (duration-of-action) and Visit 4 (onset-of-action) in terms of ocular itching score.

5.2 Collective Evidence

For the primary efficacy endpoint of ocular itching score, the three studies (11-100-0012, 13-100-0002, and 12-100-0006) demonstrated statistical superiority of cetirizine to vehicle at each of the post-CAC evaluation time point (3-, 5-, and 7-minute) on Visit 3B (duration-of-action) and Visit 4 (onset-of-action).

Table 24: Summary of Ocular Itching Scores (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score Time Post-CAC			Treatment Difference (95% CI) ¹ p-value ² Time Post-CAC		
				3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	Cetirizine	46/44	15 min	0.71	1.01	1.00	-1.47	-1.31	-1.10
	Vehicle	45/45		2.18	2.31	2.10	(-1.82, -1.12)	(-1.66, -0.95)	(-1.48, -0.72)
							<0.0001	<0.0001	<0.0001

	Cetirizine	46/44	16 hours	1.71	1.88	1.76	-0.64	-0.62	-0.46
	Vehicle	45/45		2.34	2.50	2.22	(-0.95, -0.33) 0.0003	(-0.95, -0.29) 0.0004	(-0.84, -0.08) 0.0184
12-100-0006	Cetirizine	50/49	15 min	1.00	1.18	1.11	-1.38	-1.25	-1.00
	Vehicle	50/47		2.38	2.43	2.11	(-1.72, -1.05) <0.0001	(-1.58, -0.91) <0.0001	(-1.35, -0.65) <0.0001
	Cetirizine	50/49	8 hours	1.76	1.85	1.54	-0.93	-0.89	-0.99
	Vehicle	50/47		2.69	2.74	2.53	(-1.26, -0.61) <0.0001	(-1.24, -0.54) <0.0001	(-1.40, -0.59) <0.0001
13-100-0002	Cetirizine	51/43	15 min	1.01	1.17	1.15	-1.53	-1.34	-1.07
	Vehicle	50/44		2.54	2.51	2.23	(-1.92, -1.15) <0.0001	(-1.71, -0.97) <0.0001	(-1.46, -0.69) <0.0001
	Cetirizine	51/43	8 hours	1.94	2.03	1.82	-0.92	-0.90	-0.84
	Vehicle	50/44		2.86	2.94	2.66	(-1.25, -0.58) <0.0001	(-1.23, -0.57) <0.0001	(-1.21, -0.48) <0.0001

* Post study drug instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

² P-value calculated using a two-sample t-test comparing active treatment to vehicle at each individual time point.

Source: Table 5 of Summary of Clinical Efficacy, Table 9 of Study 11-100-0012 Report, Table 9 of Study 12-100-0006 Report, and Tables 9 and 10 of Study 13-100-0002 Report.

For the co-primary efficacy endpoint of conjunctival redness scores, Studies 11-100-0012 and 12-100-0006 failed to demonstrate statistical superiority of cetirizine to vehicle at both the onset and duration-of-action CAC evaluations. Studies 13-100-0002 failed to demonstrate statistical superiority of cetirizine to vehicle at onset-of-action evaluation; at the 8-hour duration-of-action evaluation, conjunctival redness scores were significantly lower in the cetirizine group compared to vehicle group.

Table 25: Summary of Conjunctival Redness Scores (ITT, LOCF)

Study	Treatment	N Enrolled/ Completed	CAC*	Mean Score			Treatment Difference (95% CI) ¹		
				Time Post-CAC			Time Post-CAC		
				7 min	15 min	20 min	7 min	15 min	20 min
11-100-0012	Cetirizine	46/44	15 min	2.02	2.23	2.28	-0.03	0.09	0.10
	Vehicle	45/45		2.05	2.13	2.18	(-0.34, 0.27)	(-0.20, 0.39)	(-0.19, 0.40)
	Cetirizine	46/44	16 hours	1.72	1.96	1.92	-0.22	-0.06	-0.06
	Vehicle	45/45		1.94	2.02	1.98	(-0.55, 0.11)	(-0.39, 0.27)	(-0.38, 0.26)
12-100-0006	Cetirizine	50/49	15 min	1.66	1.93	1.95	-0.33	-0.03	-0.01
	Vehicle	50/47		1.98	2.09	2.09	(-0.53, -0.06)	(-0.26, 0.19)	(-0.26, 0.23)
	Cetirizine	50/49	8 hours	1.97	2.30	2.30	-0.30	-0.03	-0.01
	Vehicle	50/47		2.27	2.34	2.32	(-0.53, -0.06)	(-0.26, 0.19)	(-0.26, 0.23)
13-100-0002	Cetirizine	51/43	15 min	1.92	2.19	2.15	-0.46	-0.18	-0.25
	Vehicle	50/44		2.38	2.37	2.41	(-0.73, -0.19)	(-0.43, 0.07)	(-0.51, 0.00)
	Cetirizine	51/43	8 hours	1.97	2.13	2.09	-0.42	-0.24	-0.31
	Vehicle	50/44		2.39	2.38	2.40	(-0.68, -0.16)	(-0.49, 0.00)	(-0.58, -0.05)

* Post study drug instillation.

¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. 95% CI was based on normal approximation.

Source: Table 6 of Summary of Clinical Efficacy.

According to the protocol-defined clinical criteria for efficacy, to demonstrate efficacy at a visit, cetirizine needed to show clinical superiority over vehicle by a mean difference of at least 0.5 units of a 5 point scale for all post-CAC time points, and by at least 1 unit for the majority of the

post-CAC time points (i.e. 2 out of 3) for ocular itching. For all three studies, at Visit 4, mean treatment differences were greater than 1 unit for all time points, and all treatment differences were statistically significant, and thus the clinical criteria for efficacy were met at Visit 4 for ocular itching. However, at Visit 3B, the clinical criteria for efficacy were not met for all three studies; post-CAC mean treatment differences were less than 1 unit for all of the three time points in Studies 11-100-0012, 12-100-0006 and 13-100-0002.

The statistical reviewer analyzed the percentage of subjects with 1 unit improvement from baseline in ocular itching scores in each study. Other than the 7-minute post-CAC at Visit 3B (16-hour duration-of-action) in Study 11-100-0012, the results of this responders analysis were statistically significant at all the other time points in both Visit 3B and Visit 4 for the three studies (Table 26).

Table 26: Percentage of Subjects with 1 Unit Improvement from Baseline in Ocular Itching Scores at Each Post-CAC Time Point (ITT, BOCF)

Study	Treatment	CAC*	n/N (Percentage)			Treatment Difference (95% CI) ¹		
			Time Post-CAC			Time Post-CAC		
			3 min	5 min	7 min	3 min	5 min	7 min
11-100-0012	Cetirizine	15 min	40/46 (87.0)	37/46 (80.4)	35/46 (76.1)	53.6% (36.8%, 70.5%)	47.1% (29.2%, 65.0%)	31.6% (12.6%, 50.7%)
	Vehicle		15/45 (33.3)	15/45 (33.3)	20/45 (44.4)			
	Cetirizine	16 hours	21/46 (45.7)	20/46 (43.5)	20/46 (43.5)	19.0% (0.0%, 38.3%)	25.7% (7.5%, 43.9%)	14.6% (-4.9%, 34.1%)
	Vehicle		12/45 (26.7)	8/45 (17.8)	13/45 (28.9)			
12-100-0006	Cetirizine	15 min	42/50 (84.0)	43/50 (86.0)	43/50 (86.0)	62.0% (46.7%, 77.3%)	58.0% (42.3%, 73.7%)	48.0% (31.5%, 64.5%)
	Vehicle		11/50 (22.0)	14/50 (28.0)	19/50 (38.0)			
	Cetirizine	8 hours	25/50 (50.0)	29/50 (58.0)	30/50 (60.0)	38.0% (21.5%, 54.5%)	36.0% (18.1%, 53.9%)	34% (15.8%, 52.2%)
	Vehicle		6/50 (12.0)	11/50 (22.0)	13/50 (26.0)			
13-100-0002	Cetirizine	15 min	39/51 (76.5)	39/51 (76.5)	40/51 (78.4)	44.5% (27.1%, 61.9%)	40.5% (22.8%, 58.2%)	32.4% (50.3%, 14.6%)
	Vehicle		16/50 (32.0)	18/50 (36.00)	23/50 (46.0)			
	Cetirizine	8 hours	26/51 (51.0)	30/51 (58.8)	35/51 (68.6)	31.0% (13.3%, 48.6%)	32.8% (14.7%, 51.0%)	42.6% (25.0%, 60.2%)
	Vehicle		10/50 (20.0)	13/50 (26.0)	13/50 (26.0)			

* Post study drug instillation.

¹ 95% CI was based on normal approximation to binomial data.

Source: Statistical Reviewer's Analyses.

5.3 Conclusions and Recommendations

The statistical reviewer concluded that although there was not enough evidence to support the superiority of cetirizine to vehicle in terms of allergic conjunctival redness scores, there was substantial statistical evidence to support the superiority of cetirizine to vehicle in terms of ocular

itching scores. Whether the results for ocular itching scores are clinically relevant is beyond the scope of this statistical review.

5.4 Labeling Recommendations

The following applicant proposed labeling for the clinical studies section appears acceptable except the changes made in red in Table 1.

“14 CLINICAL STUDIES

The efficacy of TRADENAME[®] was established in three randomized, double-masked, placebo-controlled, conjunctival allergen challenge (CAC) clinical trials in patients with a history of allergic conjunctivitis.

Onset and duration-of-action were evaluated in two of these trials in which patients were randomized to receive TRADENAME[®] or vehicle ophthalmic solutions. Patients were evaluated with an ocular itching severity score ranging from 0 (no itching) to 4 (incapacitating itch) at several time points after CAC administration. Table 1 displays data from the mean ocular itching severity scores after ocular administration of a specific antigen using the CAC model. A one unit difference compared to vehicle is considered a clinically meaningful change in the ocular itching severity score.

TRADENAME[®] demonstrated statistically significantly ^{(b) (4)} ocular itching compared to vehicle at 15 minutes and 8 hours after treatment with TRADENAME[®].

Table 1 Itching Scores in the ITT Population by Treatment Group and Treatment Difference

Statistics	Study 1				Study 2			
	15 minutes post treatment		8 hours post treatment		15 minutes post treatment		8 hours post treatment	
	TRADENAME [®] N=50	Vehicle N=50	TRADENAME [®] N=50	Vehicle N=50	TRADENAME [®] N=51	Vehicle N=50	TRADENAME [®] N=51	Vehicle N=50
3 Minute Post-CAC								
Mean	1.00	2.38	1.76	2.69	1.01	2.54	1.94	2.86
Treatment Difference (95% CI) ¹	-1.38 (-1.72, -1.05)*		-0.93 (-1.26, -0.61)*		-1.53 (-1.92, -1.15)*		-0.92 (-1.25, -0.58)*	
5 Minute Post-CAC								
Mean	1.18	2.43	1.85	2.74	1.17	2.51	2.03	1.82
Treatment Difference (95% CI) ¹	-1.25 (-1.58, -0.91)*		-0.89 (-1.24, -0.54)*		-1.34 (-1.71, -0.97)*		-0.90 (-1.23, -0.57)*	
7 Minute Post-CAC								
Mean	1.11	2.11	1.54	2.53	1.15	2.23	2.94	2.66

<i>Statistics</i>	<i>Study 1</i>				<i>Study 2</i>			
	<i>15 minutes post treatment</i>		<i>8 hours post treatment</i>		<i>15 minutes post treatment</i>		<i>8 hours post treatment</i>	
	<i>TRADENAME[®]</i> <i>N=50</i>	<i>Vehicle</i> <i>N=50</i>	<i>TRADENAME[®]</i> <i>N=50</i>	<i>Vehicle</i> <i>N=50</i>	<i>TRADENAME[®]</i> <i>N=51</i>	<i>Vehicle</i> <i>N=50</i>	<i>TRADENAME[®]</i> <i>N=51</i>	<i>Vehicle</i> <i>N=50</i>
<i>Treatment Difference (95% CI)¹</i>	-1.00 (-1.35, -0.65)*		-0.99 (-1.40, -0.59)*		-1.07 (-1.46, -0.69)*		-0.84 (-1.21, -0.48)*	
¹ Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point. * p<0.05								

”

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUNFAN DENG
09/16/2016

YAN WANG
09/16/2016
I concur.