CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208694
Priority or Standard	P
Submit Date(s)	April 18, 2016
Received Date(s)	April 18, 2016
PDUFA Goal Date	October 17, 2016
Division / Office	DTOP / OAP
Reviewer Name(s)	Lucious Lim, M.D.,M.P.H.
Review Completion Date	September 11, 2016
Established Name	cetirizine ophthalmic solution, 0.24%
(Proposed) Trade Name	Zerviate
Therapeutic Class	histamine H_1 receptor antagonist
Applicant	Nicox Ophthalmics, Inc.
Formulation(s)	Topical ophthalmic solution
Dosing Regimen	One drop in the affected eye(s) twice daily
Indication(s)	Treatment of ocular itching associated with allergic conjunctivitis
Intended Population(s)	Patients ≥ 2 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208694 is recommended for approval with the revised labeling identified in this review.

The clinical studies contained in this submission support the use of cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis.

1.2 Risk Benefit Assessment

The results from the two efficacy trials (Studies 12-100-0006 and 13-100-0002), demonstrate a statistically significant and marginally clinically significant difference between cetirizine ophthalmic solution, 0.24% and vehicle for the prevention of ocular itching associated with allergic conjunctivitis.

The most frequent ocular adverse reactions were conjunctival hyperemia (5%), instillation site pain (4%) and ocular hyperemia (2%). There were no non-ocular adverse reactions that occurred at a frequency of ≥ 1 %.

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions except the usual post-marketing collection and

reporting of adverse experiences associated with the use of the drug product.

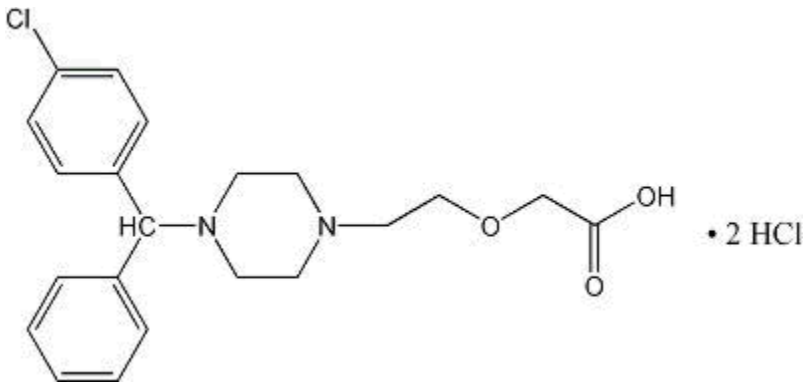
1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Chemical Structure of cetirizine



Chemical Name: (*RS*)-2-[2-[4-[(4-Chlorophenyl) phenylmethyl] piperazin-1-yl] ethoxy] acetic acid, dihydrochloride

Contains:

Active: cetirizine (b) (4) (2.4 mg/mL)

Preservative: benzalkonium chloride 0.010%

Inactives: glycerin; sodium phosphate, dibasic; edetate disodium; polyethylene glycol 400; polysorbate 80; hypromellose; hydrochloric acid/ sodium hydroxide (to adjust pH); and water for injection

Cetirizine is an antihistimine (H1-receptor antagonist) that has been developed for the treatment of ocular itching associated with allergic conjunctivitis.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved Drugs For Indication of Ocular Itching

Alocril	nedocromil	21-009
Acular	ketorolac	19-700
Optivar	azelastine	21-127
Alamast	pemirolast	21-079
Pataday	(b) (4)	21-545
Elestat	epinastine	21-565
Bepreve	bepotastine besilate	22-288
(b) (4)	alcaftadine	22-134

2.3 Availability of Proposed Active Ingredient in the United States

Cetirizine, in oral dose formulation, (Zyrtec) was approved in the United States to treat seasonal and perennial allergic rhinitis, as well as idiopathic urticarial in patients 12 years of age and older in 1995. In 2007, Zyrtec was approved for over-the-counter use.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. Common side effects seen with this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, and taster perversion/bitter taste.

There was adequate AE evaluation for cetirizine in the submitted trials.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 10, 2008, a Pre-IND meeting was held for the clinical development plan for cetirizine ophthalmic solution, X% (Pre-IND (b) (4)).

On October 5, 2010, an End-of-Phase 2 (EOP2) meeting (IND 108,558) was held to discuss (b) (4)

On September 19, 2011, a second EOP2 meeting was held to discuss the clinical development plan for cetirizine ophthalmic solution, 0.24 % for the treatment of allergic conjunctivitis.

On December 16, 2014 a Pre-NDA meeting was held to discuss the content and format of the planned 505(b)(2) NDA for cetirizine ophthalmic solution, 0.24% for the treatment of ocular itching associated with allergic conjunctivitis.

2.6 Other Relevant Background Information

Cetirizine, in oral dose formulations, (Zyrtec®; Pfizer) is approved for the treatment of seasonal and perennial allergic rhinitis, as well as idiopathic urticaria, for use in adults and pediatric patients aged 6 months and older. While originally approved in 1995 as an Rx product, Zyrtec was approved for over-the-counter use in 2007.

The clinical development program for topical ophthalmic cetirizine was initiated (b) (4). The applicant, Nicox, filed the original IND (b) (4) (IND 108,558). (b) (4) was cross referenced in the initial filing of IND 108,558.

An End-of-Phase 2 Meeting (b) (4) held on October 5, 2010, (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review for additional information.

3.2 Compliance with Good Clinical Practices

All clinical trials with cetirizine ophthalmic solution were conducted in the U.S.A., and were conducted in accordance with Good Clinical Practice (GCP).

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no principal investigators with proprietary interest or any significant financial interests in the drug product in any of the clinical studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Components and Concentrations of Cetirizine Ophthalmic Solution 0.24% Formulation

Component	Function	Reference to Quality Standards	Concentration (mg/mL)	Quantity (mg) Per Bottle 7.5-cc[c]/10-cc[d]
Cetirizine (b) (4) [a]	Active	(b) (4)	2.85 (2.40 as cetirizine (b) (4)	12.0/18.0 (cetirizine (b) (4)
Benzalkonium chloride	(b) (4) preservative		(b) (4)	(b) (4)
Glycerin	(b) (4			
Sodium phosphate, dibasic, (b) (4)				
Edetate disodium, (b) (4)				
Polyethylene glycol 400				
Polysorbate 80				
Hypromellose				

Component	Function	Reference to Quality Standards	Concentration (mg/mL)	Quantity (mg) Per Bottle 7.5-cc[c]/10-cc[d]
(b) (4) Sodium hydroxide[b]	pH adjustment	(b) (4)		(b) (4)
(b) (4) Hydrochloric acid[b]	pH adjustment			
Water for injection	(b) (4)			
(b) (4)				

[a] = Also known as Cetirizine hydrochloride, (b) (4)
[b] = Solutions prepared with Sodium Hydroxide, (b) (4), or Hydrochloric Acid, (b) (4) and Water for Injection, (b) (4).
[c] = Based on 5.0-mL fill.
[d] = Based on 7.5-mL fill.
(b) (4)

The product is sterile (b) (4) into multidose ophthalmic low-density polyethylene (LDPE) (b) (4) bottles. The packaging of the solution is provided in 2 presentations, a 5-mL fill in a 7.5-cc (b) (4) bottle, or a 7.5-mL fill in a 10-cc (b) (4) bottle, both with an LDPE (b) (4) dropper tip and polypropylene cap.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Cetirizine was not mutagenic in the Ames test or in an *in* vivo micronucleus test in rats and not clastogenic in the human lymphocyte assay or the mouse lymphoma assay.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 875 times the MRHOD on a mg/m^2).

See Pharmacology/Toxicology review for additional preclinical information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Cetirizine is a topically active, antihistamine (H1-receptor antagonist).

4.4.2 Pharmacodynamics

Refer to the Pharmacokinetics section (4.4.3) and the Pharm/Tox review.

4.4.3 Pharmacokinetics

Systemic levels of cetirizine were detected in all subjects throughout the 24 hour period following single and multiple dosing. The mean peak plasma concentration (Cmax) of cetirizine was 1.7 ng/mL after the subjects were administered a single dose of cetirizine ophthalmic solution, 0.24% to both eyes (approximately (b) (4)), and the mean peak plasma concentration (Cmax) of cetirizine was 3.1 ng/mL after the subjects were administered cetirizine to both eyes twice daily for a week. After multiple doses (one drop in each eye twice daily for a week), peak plasma concentration of cetirizine was approximatelty1.8 times higher compared to a single dose of cetirizine ophthalmic solution, 0.24%, and approximately 100 times lower than that observed following multiple oral doses of cetirizine (10 mg tablet once daily for 10 days consistent with the Zyrtec package insert).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
11-100-0004 dose - response study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.05% 0.10% 0.24% Vehicle	1 drop OU @ Visits 3A, 4A and 5 1 drop OU	6 weeks	Cetirizine 0.05%=25 0.10%=26 0.24%=25 Vehicle=25
11-100-0012 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visits 3A and 4 1 drop OU @ Visits3A and 4	Approx. 5 weeks	Cetirizine 0.24%=46 Vehicle=45
11-100-0013 safety and comfort study	Randomized, single-masked	Healthy adults	Formulation1:cetirizine 0.17% 0.24% Formulation2:cetirizine 0.24% Pataday	1 drop OD or OS 1 drop OD or OS 1 drop OD or OS	1 day	Formulation1:cetirizine 0.17%=16 0.24%=1 Formulation2:cetirizine 0.24%=15 Pataday=14

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
			Tears Naturale II	Contralateral eye		Tears Naturale II =contralateral eye
12-100-0006 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visit 3A and Visit 4 1 drop OU @ Visit 3A and Visit 4	Approx. 5 weeks	Cetirizine 0.24%=50 Vehicle=50
13-100-0002 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visit 3A and Visit 4 1 drop OU @ Visit 3A and Visit 4	Approx. 5 weeks	Cetirizine 0.24%=51 Vehicle=50
14-100-0006 safety study	Randomized, double-masked, vehicle controlled	Subjects ≥ 2 yrs old with history or family history of atopic disease	Cetirizine 0.24% Vehicle	1 drop OU BID 1 drop OU BID	Approx. 6 weeks	Cetirizine 0.24%=341 Vehicle=171
14-100-0007 PK and safety study	Open-label	Healthy adults	Cetirizine 0.24%	1 drop OU BID for 1 week	Approx. 1 week	Cetirizine 0.24%=11

5.2 Review Strategy

The submitted clinical study report and protocol for the studies identified in section 5.1 above were reviewed and formed the primary basis of safety and efficacy for this application. Studies 11-100-0004, 11-100-0012, 12-100-0006, and 13-100-0002 were used in the efficacy analysis. In addition to the studies used in the efficacy analysis, Studies 11-100-0013, 14-100-0006, and 14-100-0007001 were used in the safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials

Study 11-100-0004 - Dose Response Study

Title: A Single Center, Double-masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Efficacy of Three Different Concentrations of Cetirizine (0.05%, 0.10%, and 0.24%) Ophthalmic Solution versus Vehicle in the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model (CAC)

Study Design

This study was a prospective, single center, double-masked, vehicle-controlled, parallel group study designed to compare the safety and efficacy of three concentrations of cetirizine (0.05%, 0.10%, and 0.24%) with placebo (vehicle) in patients with a history of allergic conjunctivitis. A total of 101 patients were enrolled and 94 completed the study. Patients received masked study medication at Visit 3A (Day 0), Visit 4A (Day 14±3), and Visit 5 (Day 21±3). CAC was administered 16 hours after the Visit 3A dose and 24 hours after the Visit 4A dose to evaluate duration of action. To evaluate onset of action, CAC was administered 15 minutes after the Visit 5 dose.

Schedule of Visits and Assessments

Procedure	Visit 1 (Day -21± 3)	Visit 2 (Day-14±3)	Visit 3 (Day 0)		Visit 4 (Day 14±3)		Visit 5 (Day 21±3)	Early Exit Visit
			3A	3B (15.5 hrs from 3A)	4A	4B (23.5 hrs from 4A)		
Informed Consent/Assent HIPAA	X							
Demographic Data	X							
Medical and Medication History	X							
Medical and Medication History Update		X	X		X		X	X
Urine Pregnancy Test	X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X
Distance Visual Acuity	X	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X	X	X
Dilated fundoscopy[2]	X						X	X
Conjunctival Allergen Challenge (CAC)	X[3]	X[4]		X[5]		X[6]	X[7]	
Baseline/ Pre-CAC Sign and Symptom Assessments	X	X	X	X	X	X	X	
Post-CAC Sign and Symptom Assessments		X[8]		X[8]		X[8]	X[8]	
Randomization of study subjects			X					
In-Office Study Medication Instillation			X[9]		X		X	
Drop Comfort Assessment[10]			X					
Adverse Event Assessment	X	X	X	X	X	X	X	X
Exit Safety Exam							X[11]	
Exit from Study							X	

1 For females who were premenarchal at visit 1 and became menarchal thereafter
2 Dilated fundoscopy was performed following CAC assessments.
3 Titration CAC
4 Confirmation CAC
5 Sixteen (16) hours (+1 hour) post-medication instillation
6 24 hours (+1 hour) post-medication instillation
7 Fifteen (15) minutes post-medication instillation
8 Assessments at 3, 5, 7, 15 and 20 minutes Post-CAC
9 Only for randomized subjects
10 Upon instillation, 1 minute, and 2 minute post-instillation. At 3 minutes, subject was asked to choose 3 descriptor words to describe drops
11 Visual acuity and biomicroscopy exams was performed following the last post-CAC assessment

Inclusion Criteria

Subjects must:

1. have been at least 10 years of age of either sex and any race;
2. have provided written informed consent and signed HIPAA form. Subjects who were under the age of 18 needed to sign an assent form as well as have a parent or legal guardian sign an informed consent;
3. have been willing and able to follow all instructions and attend all study visits;
4. (for females capable of becoming pregnant) have agreed to have urine pregnancy testing performed at each visit. The subject must have chosen an acceptable method of birth control in order to continue in the study; must not have been lactating; and must have agreed to use a medically acceptable form of birth control (spermicide with barrier, oral contraceptive, injectable or implantable method) throughout the study duration and for at least 14 days prior to the first dose of study medication (Visit 3A) and for one month after the last dose of study medication. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. have had a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, dog dander, dust mites, and/or cockroaches), tree or grass pollen (white birch, oak, maple, Kentucky blue grass, rye grass, Bermuda grass, and/or Timothy grass) within the past 24 months;
6. have had a calculated best-corrected visual acuity of 0.7 logMar or better in each eye as measured using an ETDRS chart;
7. have had a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in the conjunctival vessel bed) within 10 minutes of instillation of the last titration of allergen at Visit 1;
8. have had a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in the conjunctival vessel bed) for at least two out of three time points at Visit 2;
9. have been able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion #7);
10. have avoided wearing contact lenses for at least three (3) days prior to and during the study trial period.

Exclusion Criteria

Subjects may not:

1. have had known contraindications or sensitivities to the use of any of the study medications(s) or their components;
2. have had any ocular condition that, in the opinion of the investigator, could have affected the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
4. have had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. have had the presence of an active ocular infection (bacterial, viral or fungal), positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit;
6. have manifested signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2 or 3A (defined as the presence of any itching or >1 redness in any vessel bed);
7. have used any of the following disallowed medications during the period indicated prior to Visit 1 and during the study:
   - systemic or ocular H1 antihistamine, H1 antihistamine- vasoconstrictor drug combinations: 7 days
   - decongestants: 7 days
   - monoamine oxidase inhibitors: 7 days
   - all other topical ophthalmic preparations (including artificial tears): 7 days
   - lid scrubs: 7 days
   - prostaglandins or prostaglandin derivatives: 7 days
   - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs): 7 days
   - inhaled, ocular or topical corticosteroids or mast cell stabilizers: 14 days
   - depo-corticosteroids: 45 days
   - immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage was changed during the clinical trial.

   Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Opcon-A®) may have been administered to subjects at the end of each visit, after all evaluations were completed.
8. have had a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
9. have had planned surgery (ocular or systemic) during the trial period or within 30 days after;
10. have used an investigational drug or device within 30 days of the study or be concurrently enrolled in another investigational drug or device study within 30 days of the study;
11. have been a female who was currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for

at least 14 days prior to the first dose of study medication and for one month after the last dose of study medication, or had a positive urine pregnancy test at Visit 1;

12. have had any significant illness the investigator felt could have interfered with the subject's safety or study parameters and/or put the subject at any unnecessary risk.

Primary Efficacy Variable

The co-primary efficacy variables were ocular itching (at 3, 5, and 7 minutes post-CAC) and conjunctival redness (at 7, 15, and 20 minutes post-CAC) at Visit 3B for 24 hour duration, 4B for 16 hour duration and Visit 5 for 15-minute onset of action.

To demonstrate clinical efficacy at a visit, cetirizine ophthalmic solution, 0.24% had 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 both ocular itching and conjunctival redness.

Investigators

The study was completed at one site with one principal investigator:

Investigator	**Site Number**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
Gail Torkildsen, MD Ora, Inc. 300 Brickstone Square, Third Floor Andover, MA, USA 01810 and Andover Eye Associates 138 Haverhill St. Andover, MA 01810	1	100 (50/50)

Study 11-100-0012

Title: A Multi-Center, Double-masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Cetirizine 0.24% Ophthalmic Solution (Formula AFH-002) Compared to Vehicle (Formula AFH-001) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

Study Design

This study was a prospective, multi-center, double-masked, vehicle-controlled, parallel group study designed to compare the safety and efficacy of cetirizine 0.24% with placebo (vehicle) in patients with a history of ocular allergies. A total of 91 patients were enrolled and 89 completed the study. Randomization was at a ratio of 1:1 (cetirizine:vehicle). Patients received masked study medication at Visit 3A (Day 0) and Visit 4 (Day 14±3). CAC was administered 16 hours after the Visit 3A dose to evaluate duration of action and 15 minutes after the Visit 4 dose to evaluate onset of action.

Schedule of Visits and Assessments

Procedure	**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 fundoscopy[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] Sixteen (16) 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] Sixteen (16) hours (+1 hour) post-instillation
[7] Fifteen (15) minutes post-instillation
[8] Dilated fundoscopy will be performed following CAC assessments.
[9] Relief drops will be 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.

Inclusion Criteria

To be considered for entry into the study, subjects must have met all of the following inclusion criteria:

1. Was at least 10 years of age of either sex and any race;
2. Provided written informed consent and sign the HIPAA form. Subjects who were under the age of 18 needed to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. Was willing and able to follow all instructions and attend all study visits;
4. For females capable of becoming pregnant, agreed to have urine pregnancy testing performed at screening (must be negative) and at exit visit1; must not be lactating; and must have agreed to use a medically acceptable form of birth control2 throughout the study duration and for one month after the last dose of study medication. Women considered capable of becoming pregnant included all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. 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;
6. Had a calculated best-corrected visual acuity of 0.7 logMar or better in each eye as measured using an ETDRS chart;
7. 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;
8. 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;
9. Was able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 7);
10. Was able and willing to avoid wearing contact lenses for at least 72 hours prior to and during the study trial period.

1 For premenarchal females identified at Visit 1, their menarchal status was queried at each subsequent visit. If a subject was no longer premenarchal at any of the subsequent visits, a pregnancy test was given.
The subject must have chosen an acceptable method of birth control as specified in inclusion criterion 4 in order to continue in the study.
2 Acceptable forms of birth control were spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence was considered an acceptable form of birth control.

Exclusion Criteria

Subjects must not have:

1. Had known contraindications or sensitivities to the use of any of the study medications(s) or their components;
2. Had any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. Had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
4. Had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. Had the presence of an active ocular infection (bacterial, viral or fungal) or a positive history of an ocular herpetic infection, or preauricular lymphadenopathy at Visits 1, 2, and 3A;
6. Manifested signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, and 3A (defined as the presence of any itching or > 1 [greater than 1] redness in any vessel bed);
7. Used any of the following disallowed medications during the period indicated prior to Visit 1, 2, and 3A:
    - systemic or ocular H1 antihistamine, H1 antihistamine/mast cell stabilizers, H1antihistamine- vasoconstrictor drug combinations:72 hours
    - decongestants: 7 days
    - monoamine oxidase inhibitors: 7 days
    - all other topical ophthalmic preparations (including artificial tears): 7 days
    - lid scrubs: 7 days
    - prostaglandins or prostaglandin derivatives: 7 days
    - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs): 7 days
    - inhaled, ocular or topical corticosteroids or mast cell stabilizers: 14 days
    - depo-corticosteroids: 45 days
    - immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

    Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. antihistamine/

vasoconstrictor combination products such as Visine-A™) were administered to subjects at the end of Visit 1 and may have been administered to subjects as needed at the end of Visits 2, 3B, and 4, after all evaluations are completed.

8. Had a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
9. Had planned surgery (ocular or systemic) during the trial period or within 30 days after;
10. Used an investigational drug or device within 30 days of the study or be concurrently enrolled in another investigational drug or device study within 30 days of the study;
11. Been a female who was currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for one month after the last dose of study medication, or had a positive urine pregnancy test at Visit 1;
12. Had any significant illness the investigator felt could interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk.

Primary Efficacy Variable

The co-primary efficacy variables were:

Ocular Itching: Subjects assessed ocular itching in each eye using a 5-point scale where 0 = None (normal, no itching), 1 = Intermittent tickle sensation, 2 = Mild continuous itch, 3 = Severe itch, and 4 = Incapacitating itch; 0.5 unit increments were allowed.

Conjunctival Redness: The investigator assessed conjunctival redness in each eye using a 5-point scale where 0 = None (normal, no dilated blood vessels), 1 = Mild (slightly dilated blood vessels), 2 = Moderate (more apparent dilation, with redder color, involving majority of the vessel bed), 3 = Severe (numerous and obvious dilated blood vessels, with deep red color and no chemosis, or less red with chemosis), and 4 = Extremely Severe (large, numerous, dilated blood vessels characterized by unusually severe deep red color regardless of chemosis and involving the entire vessel bed); 0.5 unit increments were allowed.

To demonstrate clinical efficacy at a visit, cetirizine 0.24% ophthalmic solution had 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 both ocular itching and conjunctival redness.

Secondary Efficacy Variables

- Ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Chemosis evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)

- Eyelid swelling evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-3 scale, NOT allowing half-unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Tearing evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, NOT allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, NOT allowing half-unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- A composite score of presence or absence of at least one nasal symptom evaluated by the subject at 7, 15, and 20 minutes post-challenge at Visits 3B (Day 0) and 4 (Day 14).

Investigators

Investigator	**Site Number**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
Gail Torkildsen, MD Andover Eye Associates 138 Haverhill St Andover, MA 01810	1	40 (21/19)
Stacey Ackerman, MD Philadelphia Eye Associates 1703 S. Broad St Philadelphia, PA 19148	2	36 (18/18)
Jack Greiner, DO Charles River Eye Associates 955 Main St Winchester, MA 01890	3	15 (7/8)

Study 12-100-0006

Title: A Single-Center, Double-masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Cetirizine 0.24% Ophthalmic Solution (Formula AFH-002) Compared to Vehicle (Formula AFH-001) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

Study Design

This study was a prospective, single-center, double-masked, vehicle-controlled, parallel group study designed to compare the safety and efficacy of cetirizine 0.24% with placebo (vehicle) in patients with a history of allergic conjunctivitis. A total of 100 patients were enrolled and 97 completed the study. Randomization was at a ratio of 1:1 (cetirizine:vehicle). Patients received masked study medication at Visit 3A (Day 0) and Visit 4 (Day 14±3). CAC was administered 8 hours after the Visit 3A dose to evaluate duration of action and 15 minutes after the Visit 4 dose to evaluate onset of action.

Schedule of Visits and Assessments

Procedure	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 fundoscopy[8]	X				X
Instillation of Relief Drops[9]	X	X		X	X
Adverse Event Query	X	X	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] Eight (8) hours (+30 minutes) 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] Eight (8) hours (+30 minutes) post-instillation
[7] Fifteen (15) minutes post-instillation
[8] Dilated fundoscopy was performed following CAC assessments.
[9] Relief drops administered at Visit 1 and may have been administered at Visits 2, 3B, and 4 after all assessments are complete. Instillation information was recorded on the concomitant medication page.

Inclusion Criteria

To be considered for entry into the study, subjects must have:

1. been at least 10 years of age of either sex and any race;
2. provided written informed consent and signed the HIPAA form. Subjects who were under the age of 18 were required to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. been willing and able to follow all instructions and attend all study visits;
4. for females capable of becoming pregnant, agreed to have urine pregnancy testing performed at screening (must have been negative) and at exit visit[1]; must not have been lactating; and must have agreed to use a medically acceptable form of birth control[2] throughout the study duration and for one month after the last dose of study medication. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. 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;
6. had a calculated best-corrected visual acuity of 0.7 logMar or better in each eye as measured using an ETDRS chart;
7. had a positive bilateral CAC reaction (greater than or equal to a 2 itching and greater than or equal to a 2 conjunctival redness) within 10 minutes of instillation of the last titration of allergen at Visit 1;
8. had a positive bilateral CAC reaction (greater than or equal to a 2 itching and greater than or equal to a 2 conjunctival redness) for at least two out of three time points at Visit 2;
9. been able and willing to avoid all disallowed medications for the appropriate washout period and during the study (see exclusion 7);
10. been able and willing to avoid wearing contact lenses for at least 72 hours prior to and during the study trial period.

1 For premenarchal females identified at Visit 1, their menarchal status was queried at each subsequent visit. If a subject was no longer premenarchal at any of the subsequent visits, a pregnancy test was given. The subject must have chosen an acceptable method of birth control as specified in inclusion criterion 4 in order to continue in the study.
2 Acceptable forms of birth control were spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence was considered an acceptable form of birth control.

Exclusion Criteria

Subjects may not have:

1. had known contraindications or sensitivities to the use of any of the study medications(s) or their components;
2. had any ocular condition that, in the opinion of the investigator, could have affected the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
4. had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. had the presence of an active ocular infection (bacterial, viral or fungal) or a positive history of an ocular herpetic infection, or preauricular lymphadenopathy at Visits 1, 2, and 3A;
6. manifested signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, and 3A (defined as the presence of any itching or >1 [greater than 1] redness in any vessel bed);
7. used any of the following disallowed medications during the period indicated prior to Visit 1, 2, and 3A:
    - systemic or ocular H1 antihistamine, H1 antihistamine/mast cell stabilizers, H1 antihistamine-vasoconstrictor drug combinations:72 hours
    - decongestants: 7 days
    - monoamine oxidase inhibitors: 7 days
    - all other topical ophthalmic preparations (including artificial tears): 7 days
    - lid scrubs: 7 days
    - prostaglandins or prostaglandin derivatives: 7 days
    - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs): 7 days
    - inhaled, ocular or topical corticosteroids or mast cell stabilizers: 14 days
    - depo-corticosteroids: 45 days
    - immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e., antihistamine/vasoconstrictor combination products such as Visine®-A®) were administered to subjects at the end of Visit 1 and may have been administered to subjects at the end of Visits 2, 3B, and 4, after all evaluations were completed.

8. had a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
9. had planned surgery (ocular or systemic) during the trial period or within 30 days after;

10. used an investigational drug or device within 30 days of the study or have been concurrently enrolled in another investigational drug or device study within 30 days of the study;
11. been a female who was, at the time of the study, pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for one month after the last dose of study medication, or had a positive urine pregnancy test at Visit 1;
12. had any significant illness the investigator felt could interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk.

Primary Efficacy Variable

The co-primary efficacy variables were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post-challenge (0-4 scale, allowing half unit increments) at Visit 3B (Day 0) and Visit 4 (Day 14)
- Conjunctival redness evaluated by the investigator at 7, 15, 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visit 3B (Day 0) and Visit 4 (Day 14)

To demonstrate clinical efficacy at a visit, cetirizine 0.24% ophthalmic solution had 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 both ocular itching and conjunctival redness.

Secondary Efficacy Variables

- Ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Chemosis evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Eyelid swelling evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-3 scale, NOT allowing half-unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Tearing evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, NOT allowing half unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, NOT allowing half-unit increments) at Visits 3B (Day 0) and 4 (Day 14)
- A composite score of presence or absence of at least one nasal symptom evaluated by the subject at 7, 15, and 20 minutes post-challenge at Visits 3B (Day 0) and 4 (Day 14)

Investigators

The study was completed at one site with one principal investigator:

Investigator	**Site Number**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
Gail Torkildsen, MD Andover Eye Associates 138 Haverhill St. Andover, MA 01810	1	100 (50/50)

See Section 6 for efficacy results and Section 7 for safety.

Study 13-100-0002

Title: A Multi-Center, Double-masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Cetirizine 0.24% Ophthalmic Solution (Formula AFH-002) Compared to Vehicle (Formula AFH-001) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

Study Design

This study was a prospective, multi-center, double-masked, vehicle-controlled, parallel group study designed to compare the safety and efficacy of cetirizine 0.24% with placebo (vehicle) in patients with a history of allergic conjunctivitis. A total of 101 patients were enrolled and 87 completed the study. Randomization was at a ratio of 1:1 (cetirizine:vehicle). Patients received masked study medication at Visit 3A (Day 0) and Visit 4 (Day 14±3). CAC was administered 8 hours after the Visit 3A dose to evaluate duration of action and 15 minutes after the Visit 4 dose to evaluate onset of action.

Schedule of Visits and Assessments

Procedure	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[3]	X[4]			
Randomization of study subjects			X		
Study Drug or Vehicle Instillation			X[5]		X[6]
In-Office Drop Comfort Assessments[7]			X		
Drop Efficacy Conjunctival				X[8]	X[9]

Procedure	Visit 1 (Day -21 ± 3)	Visit 2 (Day -14 ± 3)	Visit 3 (Day 0)		Visit 4 (Day 14 ± 3)
			3A	3B	
Allergen Challenge					
Dilated fundoscopy[10]	X				X
Instillation of Relief Drops[11]	X	X		X	X
Adverse Event Query	X	X	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] Titration CAC
[4] Confirmation CAC
[5] Eight (8) hours (+30 minutes) before Visit 3B CAC
[6] Fifteen (15) minutes pre-CAC
[7] Included comfort (immediately, 1 and 2 minutes post-instillation) and drop descriptor word queries (3 minutes post-instillation)
[8] Eight (8) hours (+30 minutes) post-instillation
[9] Fifteen (15) minutes post-instillation
[10] Dilated fundoscopy was performed following CAC assessments.
[11] Relief drops were to be administered at Visit 1 and could have been administered at Visits 2, 3B, and 4 after all assessments were complete.

Inclusion Criteria

To be considered for entry into the study, subjects must have:

1. been at least 10 years of age of either sex and any race;
2. provided written informed consent and sign the HIPAA form. Subjects who were under the age of 18 were required to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. been willing and able to follow all instructions and attend all study visits;
4. for females capable of becoming pregnant, agreed to have urine pregnancy testing performed at screening (must be negative) and at exit visit; not have been lactating; and agreed to use a medically acceptable form of birth control throughout the study duration and for one month after the last dose of either study drug or vehicle. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. 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;
6. had a calculated best-corrected visual acuity of 0.7 logMar or better in each eye as measured using an ETDRS chart;
7. had a positive bilateral CAC reaction (≥ 2 [greater than or equal to a 2] itching and ≥ 2 [greater than or equal to a 2] conjunctival redness) within 10 minutes of instillation of the last titration of allergen at Visit 1;

8. had a positive bilateral CAC reaction (≥ 2 [greater than or equal to a 2] itching and ≥ 2 [greater than or equal to a 2] conjunctival redness) for at least two out of three time points at Visit 2;
9. had an average of >2.5 [greater than 2.5] itching and >0.5 [greater than 0.5] eyelid swelling for both eyes after post-CAC assessments at Visit 2;
10. been able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 7);
11. been able and willing to avoid wearing contact lenses for at least 72 hours prior to and during the study trial period.

Exclusion Criteria

Subjects may not have:

1. had known contraindications or sensitivities to the use of any of either the study drug or vehicle or their components;
2. had any ocular condition that, in the opinion of the investigator, could have affected the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the prior 6 months;
4. had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. had the presence of an active ocular infection (bacterial, viral or fungal) or a positive history of an ocular herpetic infection, or preauricular lymphadenopathy at Visits 1, 2, and 3A;
6. manifested signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, and 3A (defined as the presence of any itching or >1[greater than 1] redness in any vessel bed);
7. used any of the following disallowed medications during the period indicated prior to Visit 1, 2, and 3A:
    - systemic or ocular H1 antihistamine, H1 antihistamine/mast cell stabilizers, H1 antihistamine- vasoconstrictor drug combinations: 72 hours
    - decongestants: 7 days
    - monoamine oxidase inhibitors: 7 days
    - all other topical ophthalmic preparations (including artificial tears): 7 days
    - lid scrubs: 7 days
    - prostaglandins or prostaglandin derivatives: 7 days
    - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin and aspirin containing products: 7 days
    - inhaled, ocular or topical corticosteroids or mast cell stabilizers: 14 days
    - depo-corticosteroids: 45 days
    - immunotherapeutic agents: treatment must have been maintained steadily for at least 2 months; neither the immunotherapeutic agent nor its dosage changed during the

clinical trial.

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e., antihistamine/vasoconstrictor combination products such as Visine®-A®) were to be administered to subjects at the end of Visit 1 and may have been administered to subjects at the end of Visits 2, 3B, and 4, after all evaluations were completed.

8. had a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
9. planned surgery (ocular or systemic) during the trial period or within 30 days after;
10. used an investigational drug or device within 30 days of the study or been concurrently enrolled in another investigational drug or device study within 30 days of the study;
11. been a female who was currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for one month after the last dose of either study drug or vehicle, or had a positive urine pregnancy test at Visit 1;
12. had any significant illness the investigator feels could have interfered with the subject's safety or study parameters and/or put the subject at any unnecessary risk.

Primary Efficacy Variable

The primary efficacy co-variables were:

- Ocular itching assessed by the subject at 3(±1), 5(±1), and 7(±1) minutes post-challenge (0-4 scale, allowing half unit increments) at Visit 3B (Day 0) and Visit 4 (Day 14)
- Conjunctival redness assessed by the investigator at 7(±1), 15(±1), 20(±1) minutes post-challenge (0-4 scale, allowing half unit increments) at Visit 3B (Day 0) and Visit 4 (Day 14)

To demonstrate clinical efficacy at a visit, cetirizine 0.24% ophthalmic solution had 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 both ocular itching and conjunctival redness.

Secondary Efficacy Variables

- Ciliary and Episcleral Redness: At Visits 3B and 4, the investigator separately assessed ciliary and episcleral redness with a slit lamp at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Chemosis: At Visits 3B and 4, the investigator assessed chemosis with a slit lamp at 7(±1), 15(±1) and 20(±1) minutes post-challenge.
- Eyelid Swelling: At Visits 3B and 4, subjects self-assessed eyelid swelling at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Tearing: At Visits 3B and 4, subjects self-assessed tearing at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Individual Nasal Allergy Symptoms: At Visits 3B and 4, subjects self-assessed rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion at 7(±1), 15(±1) and 20(±1) minutes post-challenge.
- Composite Nasal Symptom Score: For Visits 3B and 4, binary composite scores for presence or absence of at least one nasal symptom were derived for the time points 7(±1), 15(±1), and 20(±1) minutes post-challenge by study statisticians using the individual nasal allergy symptom scores reported by each subject.

Tolerability Variables

- **Drop Comfort Assessment:** At visit 3A, subjects self-assessed comfort immediately upon instillation, 1 minute post-instillation, and 2 minutes post-instillation by selecting a value on numerical scale ranging from 0–10, wherein 0 = *very comfortable* and 10 = *very uncomfortable*.
- **Drop Descriptor Query:** At Visit 3A, subjects selected 3 words from a list of 12 words which best described the sensation in both eyes at 3 minutes post-instillation.

Subjects were also allowed to provide their own descriptor words.

Investigators

Investigator	**Site Number**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
Eugene McLaurin, MD Total Eye Care 6060 Primacy Parkway Suite 200 Memphis, TN 38119	1	67 (34/33)
Mark Bergmann, MD Eye Care Associates of Greater Cincinnati 2859 Boudinot Ave. Suite 301 Cincinnati OH 45238 **Current Address:** Apex Eye 6507 Harrison Ave, Ste E Cincinnati, OH 45247	2	22 (11/11)
Edward Meier, MD Eye Care Associates of Greater Cincinnati 6394 Thornberry Court, Suite 810 Mason, OH 45040	3	12 (6/6)

See Section 6 for efficacy results and Section 7 for safety.

Study 14-100-0006 - Safety Study

Title: A Multi-Center, Double-masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Cetirizine 0.24% Ophthalmic Solution Used Twice Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Acute Allergic Conjunctivitis)

Study Design

This study was a prospective, multi-center, double-masked, vehicle-controlled, parallel group study designed to compare the safety and tolerability of cetirizine 0.24% versus its vehicle in healthy adult subjects and in pediatric subjects (≥2 years to ≤10 years) with a history of atopic disease (including allergic conjunctivitis). A total of 512 subjects were enrolled and 488 completed the study. Fifty-nine (59) were pediatric subjects. Randomization was at a ratio of

2:1 (cetirizine:vehicle). Study received one (1) drop of study drug or vehicle OU twice daily (BID) for up to 6 weeks.

Schedule of Visits and Assessments

Assessment	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Visit 5 [1]
	Day 1	Day 8 ± 2	Day 22 ± 3	Day 43 + 3	Day 85 +7
Informed Consent/Assent/HIPAA[2]	X				
Demographics	X				
Medical/Medication/Ocular History	X				
Medical and Medication History Update		X	X	X	X
Urine Pregnancy Test[3]	X	X	X	X	X
Body Weight Determination[4]	X				
Physical Exam[5]	X			X	X
Vital Signs (resting blood pressure and pulse)	X			X	X
Visual Acuity[6]	X	X	X	X	X
Slit lamp biomicroscopy[7]	X	X	X	X	X
Intraocular Pressure[8]	X			X	X
Dilated Ophthalmoscopy	X			X	X
Specular Microscopy (Ocular Endothelial Cell Counts)[9]	X[10]			X	X
Enrollment/Randomization	X				
In-Office Study Drug or Vehicle Instillation	X[11]	X[12]	X[12]		
Drop Comfort Assessment[13]	X	X	X		
Dispensation of Study Drug or Placebo & Dosing Diary	X	X	X		

Assessment	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Visit 5 [1]
	Day 1	Day 8 ± 2	Day 22 ± 3	Day 43 + 3	Day 85 +7
Collection of Returned Study Drug or Vehicle & Dosing Diary[14]		X	X	X	
Assessment of Adverse Events	X	X	X	X	X
Exit				X	X

[1] Only attended by subjects who underwent ocular endothelial cell count procedures
[2] Assent was provided by subjects who were at least 7 years of age and less than 18 years of age.
[3] Conducted on females of child bearing potential. At Visits 2 and 3, a urine pregnancy test was conducted for females who were premenarchal at the previous visit and became menarchal thereafter.
[4] The Investigator referred to Protocol Appendix 4 [*Table of Fifth (5th) Percentile Body Weights by Age*] for subjects <12 years of age only.
[5] Physical Examination included general health, head, eyes, ears, nose, throat (HEENT), and any other comments.
[6] For subjects under 10 years of age who were developmentally unable to use ETDRS chart, a best attempt at obtaining visual acuity was made by using a LEA symbols visual acuity chart. For subjects evaluated by LEA symbols or visual behavior, VA was measured in 20-foot Snellen equivalent units.
[7] Evaluated pre-dose and 15 minutes (+ 3 minutes) post-dose of study drug or vehicle at Visit 1, Visit 2, and Visit 3 and once at Visit 4 and Visit 5.
[8] Age > 10 years old, when possible.
[9] Limited to up to 150 subjects undergoing ocular endothelial cell counts.
[10] Prior to instillation of study drug or vehicle
[11] Subject, subject's caregiver, or subject's parent/legal guardian instilled investigational product at Visit 1 and observed by a trained study technician
[12] A trained study technician instilled study drug or vehicle OU (at least 7 hours after the previous dose instilled at home that same calendar day, if applicable).
[13] Subjects assessed comfort immediately upon instillation, at 30 seconds post-dose, and at 1 minute post-dose of study drug or vehicle using 0 – 10 scale for each eye
[14] A new dosing diary was distributed at Visits 1, 2, and 3.

Inclusion Criteria

Subjects MUST HAVE:

1. been at least 2 years of age at Visit 1 (Day 1/Baseline) of either gender and any race or ethnicity (a government issued ID and/or birth certificate was verified at the time the informed consent form [ICF] was signed);
2. provided written informed consent and signed the HIPAA form. Subjects who were at least 7 years of age and less than 18 years of age needed to sign an assent form. In addition, all subjects below the age of 18 years were required to have a parent or legal guardian sign the informed consent;
3. been willing and able to follow all instructions and attend all study visits (and been accompanied by a parent/legal guardian if the subject was under the age of 18);
4. been able to self-administer eye drops satisfactorily or have a caregiver or parent/legal guardian (if applicable, for subjects less than 18 years of age) at home[1] routinely available for this purpose. The school healthcare provider (e.g., nurse) was regarded as the caregiver for the purpose of study drug or vehicle instillation at school;

5. for subjects less than 18 years of age, had either a history or family history of atopic disease (including allergic conjunctivitis);
6. (if female and of childbearing potential) agreed to have urine pregnancy testing performed at screening (must have been negative) and at the exit visit2; not have been lactating; and agreed to use a medically acceptable form of birth control3 throughout the study duration and for at least 14 days prior to the first dose of study drug or vehicle (Visit 1/Day 1/Baseline) and for 1 month after the last dose of study drug or vehicle. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
7. had ocular health within normal limits, including a calculated visual acuity of 0.3 logMAR or better in each eye as measured using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. For subjects under 10 years old who were developmentally unable to use the ETDRS chart, a best attempt at visual acuity was made using the LEA symbols or Visual Behavior. For these subjects, 20-foot Snellen equivalent units of 20/63 or better in both eyes was required; (for selected subjects agreeing to undergo corneal endothelial cell counts) had a Baseline (Visit 1/Day 1/Baseline) corneal endothelial cell density ≥ 2200 cells/mm^2.

1 If a caregiver or parent/legal guardian was to administer eye drops, then he/she must have been present at Visit 1 to administer eye drops in-office.
2 For identified premenarchal females at Visit 1, their menarchal status was queried at each subsequent visit. If a subject was no longer premenarchal at any of her subsequent visits, then that subject must have agreed to have a urine pregnancy test performed at that visit. Subsequently these subjects followed all the requirements of female subjects of childbearing potential regarding pregnancy tests and birth control.
Subject must have agreed to use at least 1 medically acceptable form of birth control throughout the study duration and for 1 month after the last dose of investigational product.
3 Acceptable forms of birth control were abstinence, spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner.

Exclusion Criteria

Subjects MUST NOT HAVE:
1. had known contraindications or sensitivity to the use of any of the investigational product(s) or their components, or any other medications required by the protocol;
2. had ocular surgical intervention within 3 months prior to Visit 1 (Day 1/Baseline) or during the study and/or a history of refractive surgery within the prior 6 months;
3. had a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
4. had the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at Visit 1 (Day 1/Baseline);
5. used any of the following disallowed medications during the period indicated prior to Visit 1 (Day 1/Baseline) and for the duration of the study:
   - artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular corticosteroids, and any other topical ophthalmic agents (5 days);

- used contact lenses (5 days);
- received systemic corticosteroids or cancer chemotherapy, and/or any other systemic medications which the investigator felt may have confounded study data, or interfered with subject's study participation (14 days); and/or
- had current or anticipated use of any topical (including ocular and nasal) or systemic anti-allergy medications (21 days);

6. had prior (within 7 days of beginning study drug or vehicle) or currently active significant illness that could have compromised participation, in the opinion of the investigator;
7. had prior (within 30 days of beginning investigational product) or anticipated concurrent use of an investigational product or device during the study period;
8. had an ocular or systemic condition or was in a situation that the investigator felt may have put the subject at significant risk, confounded the study results, or interfered significantly with the subject's study participation;
9. had planned surgery (ocular or systemic) during the trial period or within 30 days after the study period;
10. had body weight below the 5th percentile for their age (subjects 12 years of age or younger only);
11. been currently breast feeding or planning to breast feed during the study period or was a female who was currently pregnant, planning a pregnancy, or had a positive urine pregnancy test at Visit 1 (Day 1/Baseline);
12. had an abnormal blood pressure, defined as ≤ 90 or ≥ 160 (systolic) measured in mmHg or ≤ 60 or ≥ 100 (diastolic) measured in mmHg. For pediatric subjects, abnormal blood pressure was defined as ≥ 140 (systolic) measured in mmHg or≥ 90 (diastolic) measured in mmHg;
13. had IOP that was less than 5 mmHg or greater than 22 mmHg or a normal IOP with a prior diagnosis/history of glaucoma at Visit 1 (Day 1/Baseline).

Safety Variables

The safety parameters evaluated in this study included AEs, urine pregnancy test, visual acuity, slit lamp biomicroscopy, IOP, physical examination, measurement of vital signs, dilated ophthalmoscopy, and specular microscopy for the determination of corneal endothelial cell counts and density.

Investigators

Investigator	**Site Number**	**Number of Subjects Enrolled (Cetirizine/Vehicle)**
Dawn DeCastro, MD Andover Eye Associates 138 Haverhill Street Andover, MA 01810	1	154
Edward Meier, MD Eye Care Associates of Greater	2	120

Investigator	Site Number	Number of Subjects Enrolled (Cetirizine/Vehicle)
Cincinnati 6394 Thornberry Court, Suite 810 Mason, OH 45040		
Stacey Ackerman, MD Philadelphia Eye Associates 1703 Broad Street Philadelphia, PA 19148	3	115
Eugene Protzko, MD Seidenberg Protzko Eye Associates 2023 Pulaski Hwy Havre de Grace, MD 21078	4	123

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is the treatment of ocular itching associated with allergic conjunctivitis.

6.1.1 Methods

The primary support for efficacy for cetirizine ophthalmic solution, 0.24% comes from two studies: 12-100-0006 and 13-100-0002. All the studies used the CAC model of acute conjunctivitis to determine the efficacy of cetirizine ophthalmic solution 0.24%, with CAC performed 15 minutes and 8 hours after study medication instillation.

The CAC model is a validated model that creates an allergic response similar to allergic response in an environmental setting. This model is well-accepted as a surrogate of the ocular symptoms of allergic conjunctivitis.

6.1.2 Demographics

Studies 12-100-0006 and 13-100-0002: (ITT Population)

	Single-Center CAC Study 12-100-0006			Multi-Center CAC Study 13-100-0002		
	Cetirizine 0.24% (N=50)	Vehicle (N=50)	Total Subjects (N=100)	Vehicle (N=51)	Vehicle (N=50)	Total Subjects (N=101)
Age						
N	50	50	100	51	50	101
Mean (SD)	39.5 (17.32)	38.1 (14.56)	38.8 (15.93)	40.6 (12.80)	39.2 (10.84)	39.9 (11.84)
Median	38.0	39.5	38	41.0	39.5	41.0
Min-Max	11-74	13-75	11-75	18-68	18-71	18-71
Gender						
Male	13 (26.9%)	20 (40.0%)	33 (33.0%)	12 (23.5%)	20 (40.0%)	32 (31.7%)

Female	17 (74.0%)	30 (60.0%)	67 (67.0%)	39 (76.5%)	30 (60.0%)	69 (68.3%)
Ethnicity						
Hispanic or Latino	11 (22.0%)	4 (8.0%)	15 (15.0%)	1 (2.0%)	0 (0.0%)	1 (1.0%)
Not Hispanic or Latino	39 (78.0%)	46 (92.0%)	85 (85.0%)	50 (98.0%)	50 (100.0%)	100 (99.0%)
Race						
American Indian or Alaskan Native	2 (4.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	1 (2.0%)	2 (4.0%)	3 (3.0%)	0 (0.0%)	1 (2.0%)	1 (1.0%)
Black or African American	3 (6.0%)	2 (4.0%)	5 (5.0%)	10 (19.6%)	17 (34.0%)	27 (26.7%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	44 (88.0%)	46 (92.0%)	90 (90.0%)	41 (80.4%)	31 (62.0%)	72 (71.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (1.0%)
Iris Color						
Black	2 (2.0%)	0 (0.0%)	2 (1.0%)	2 (2.0%)	4 (4.0%)	6 (3.0%)
Blue	34 (34.0%)	36 (36.0%)	70 (35.0%)	36 (35.3%)	18 (18.0%)	54 (26.7%)
Brown	38 (38.0%)	36 (36.0%)	74 (37.0%)	38 (37.3%)	60 (60.0%)	98 (48.5%)
Hazel	14 (14.0%)	14 (14.0%)	28 (14.0%)	12 (11.8%)	6 (6.0%)	18 (8.9%)
Green	12 (12.0%)	14 (14.0%)	26 (13.0%)	14 (13.7%)	12 (12.0%)	26 (12.9%)
Gray	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Study 11-100-0012: (ITT Population)

Multi-Center Study 11-100-0012			
	Cetirizine 0.24% (N=46)	Vehicle (N=45)	Total Subjects (N=91)
Age			
Mean (SD)	36.6 (14.95)	38.1 (14.08)	37.4 (14.47)
Gender			
Male, n (%)	22 (47.8)	17 (37.8)	39 (42.9)
Female, n (%)	24 (52.2)	28 (62.2)	52 (57.1)
Ethnicity			
Hispanic, n (%)	12 (26.1)	13 (28.9)	25 (27.5)
Non-Hispanic, n (%)	34 (73.9)	32 (71.1)	66 (72.5)
Race			
White	30 (65.2)	33 (73.3)	63 (69.2)
Black or African American, n (%)	9 (19.6)	5 (11.1)	14 (15.4)
Am. Indian or Alaskan Native, n (%)	7 (15.2)	7 (15.6)	14 (15.4)
Iris Color			
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)

6.1.3 Subject Disposition

The efficacy results are based on the ITT population for all randomized patients enrolled in one dose-response trial, Study 11-100-0004 and three CAC efficacy trials, Studies 11-100-0012, 12-100-0006, and 13-100-0002.

Patient Withdrawals from Dose Response and Efficacy Trials

Study	Patient ID#	Treatment	Reason for Discontinuation
11-100-0004	001-1014	Cetirizine 0.054%	Adverse Event (palatal edema and itching)
11-100-0004	001-1019	Cetirizine 0.24%	Administrative Reasons (e.g., inability to continue, lost to follow-up)
11-100-0004	001-1036	Cetirizine 0.24%	Administrative Reasons (e.g., inability to continue, lost to follow-up)
11-100-0004	001-1058	Cetirizine 0.24%	Adverse Event (epistaxis)
11-100-0004	001-1072	Cetirizine 0.10%	Other (health issues in family members)
11-100-0004	001-1084	Cetirizine 0.05%	Administrative Reasons (e.g., inability to continue, lost to follow-up)
11-100-0004	001-1098	Cetirizine 0.24%	Protocol Violation (Manifest clinically active allergic conjunctivitis at the start of Visit 5)
11-100-0012	001- 1012	Cetirizine 0.24%	Manifest clinically active signs or symptoms of allergic conjunctivitis at Visit 4
11-100-0012	001-1112	Cetirizine 0.24%	Manifest clinically active signs or symptoms of allergic conjunctivitis at Visit 4
12-100-0006	001-1016	Vehicle	Adverse Events (superficial punctate keratitis)
12-100-0006	001-1033	Vehicle	Administrative Reasons (e.g., inability to continue, lost to follow-up)
12-100-0006	001-1128	Vehicle	Manifest active signs or symptoms of allergic conjunctivitis at Visit 4
12-100-0006	001-1144	Cetirizine 0.24%	Adverse Events (intermittent general muscular pain)

Study	Patient ID#	Treatment	Reason for Discontinuation
13-100-0002	1-1010	Cetirizine 0.24%	Protocol Violations
13-100-0002	1-1011	Vehicle	Protocol Violations
13-100-0002	1-1013	Vehicle	Administrative Reasons (e.g., inability to continue, lost to follow-up)
13-100-0002	1-1016	Vehicle	Manifest active signs or symptoms of allergic conjunctivitis at Visit 4
13-100-0002	1-1017	Cetirizine 0.24%	Administrative Reasons (e.g., inability to continue, lost to follow-up)
13-100-0002	1-1020	Cetirizine 0.24%	Protocol Violations
13-100-0002	1-1021	Vehicle	Protocol Violations
13-100-0002	1-1211	Cetirizine 0.24%	Administrative Reasons (e.g., inability to continue, lost to follow-up)
13-100-0002	1-1214	Cetirizine 0.24%	Manifest active signs or symptoms of allergic conjunctivitis at Visit 4
13-100-0002	1-1217	Cetirizine 0.24%	Protocol Violations
13-100-0002	1-1218	Cetirizine 0.24%	Manifest active signs or symptoms of allergic conjunctivitis at Visit 4
13-100-0002	1-1219	Vehicle	Manifest active signs or symptoms of allergic conjunctivitis at Visit 4
13-100-0002	1-1220	Vehicle	Administrative Reasons (e.g., inability to continue, lost to follow-up)
13-100-0002	1-1226	Cetirizine 0.24%	Administrative Reasons (e.g., inability to continue, lost to follow-up)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variables for the dose-response and efficacy CAC Studies 11-100-0004, 11-100-0012, Protocol 12-100-0006, and 13-100-0002 were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit scale, allowing half unit increments)
- Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit scale, allowing half unit increments)
-

Study 11-100-004 – Primary Efficacy Endpoint Results*

Timepoint (Minutes post-CAC)	**Cetirizine Concentration**								
	0.05%	0.10%	0.24%	0.05%	0.10%	0.24%	0.05%	0.10%	0.24%
	Visit 3B (Duration 16 Hrs.)			**Visit 4B (Duration 24 Hrs.)**			**Visit 5 (Onset 15 Mins.)**		
Ocular Itching ITT w/ LOCF [Mean Difference (*P*)]									
3	-0.57 (0.01)[2]	-0.48 (0.01)[2]	-0.83 (0.001)[1]	-0.25 (0.23)[1]	-0.46 (0.03)[1]	-0.34 (0.05)[2]	-0.89 (0.001)[1]	-1.10 (<0.001)[1]	-1.03 (0.001)
5	-0.54 (0.03)[1]	-0.51 (0.02)[1]	-0.81 (0.001)[1]	-0.24 (0.16)2	-0.32 (0.16)[1]	-0.07 (0.51)[2]	-0.90 (0.001)[1]	-1.00 (0.001)[1]	-1.02 (0.001)[1]
7	-0.41 (0.09)[1]	-0.40 (0.10)[1]	-0.52 (0.03)1	-0.31 (0.11)[2]	-0.30 (0.21)[1]	-0.11 (0.62)[1]	-0.93 (0.001)[1]	-0.87 (0.001)[1]	-0.97 (0.001)[1]
Conjunctival Redness ITT w/ LOCF [Mean Difference (*P*)]									
3	-0.17 (0.25)[1]	-0.20 (0.17)[1]	-0.34 (0.007)[1]	-0.27 (0.10)[1]	-0.33 (0.06)[1]	0.01 (0.68)[2]	-0.44 (0.01)[1]	-0.43 (0.03)[1]	-0.22 (0.23)[1]
15	-0.23 (0.13)[1]	-0.26 (0.13)[1]	-0.30 (0.04)[1]	-0.27 (0.09)[1]	-0.31 (0.06)[1]	-0.05 (0.70)[1]	-0.15 (0.29)[2]	-0.29 (0.16)[1]	-0.13 (0.47)[1]
20	-0.25 (0.13)[1]	-0.30 (0.08)[1]	-0.32 (0.04)[1]	-0.15 (0.38)[1]	-0.22 (0.21)[1]	0.03 (0.62)[2]	-0.14 (0.39)[2]	-0.30 (0.17)[1]	-0.18 (0.35)

* CAC data, based on either the two-sample t- test or the Wilcoxon rank sum test, whichever gave the better p-value comparing each of the cetirizine active groups to vehicle.
1 p value calculated using a two-sample t-test comparing each treatment group to vehicle.
2 p value calculated using a Wilcoxon rank sum test comparing each treatment group to vehicle.

Reviewer's comments: *For the ocular itching endpoint, the cetirizine 0.1% and 0.24% showed statistical significance at all time points measured and clinical significance at a majority of the time points measured at Visit 5 (onset 15 minutes).*

At 16 hours, the majority of the efficacy is no longer present for the 0.1% concentration. For the 0.24%, the product was only marginally effective at 16 hours and did not demonstrate efficacy at 24 hours.

For the conjunctival redness endpoint, there was no clear trend for statistical and clinical significance among the 3 concentrations of cetirizine.

Study 11-100-0012 - Primary Efficacy Endpoint Results*

Timepoint (Minutes post-CAC)	Cetirizine 0.24% N=46	Vehicle N=45	Cetirizine 0.24% N=46	Vehicle N=45
	Visit 3B (Duration 16 Hrs.)		**Visit 4 (Onset 15 Mins.)**	
Ocular Itching ITT w/ LOCF [Mean Difference (*P*)]				
3	-0.64 (0.0003)[1]		-1.47 (<0.0001)[1]	
5	-0.62 (0.0004)[1]		-1.31 (<0.0001)[1]	
7	-0.46 (0.0184)[1]		-1.10 (<0.0001)[1]	
Conjunctival Redness ITT w/ LOCF [Mean Difference (*P*)]				
7	-0.22 (0.1819)[1]		-0.03 (0.8299)[1]	
15	-0.06 (0.7118)[1]		0.09 0.5294)[1]	
20	-0.06 (0.7073)[1]		0.11 (0.4788)[1]	

* CAC data, based on either the two-sample t- test or the Wilcoxon rank sum test, whichever gave the better p-value comparing each of the cetirizine active groups to vehicle.
1 p value calculated using a two-sample t-test comparing each treatment group to vehicle.
2 p value calculated using a Wilcoxon rank sum test comparing each treatment group to vehicle.

Reviewer's comments: *For the ocular itching endpoint, cetirizine 0.24% showed statistical and clinical significance at all time points measured at Visit 4 (onset 15 minutes). Half of the efficacy had worn off in the Cetirizine 0.24% group at 16 hours.*

For the conjunctival redness endpoint, cetirizine 0.24% failed to show statistical and clinical significance at all time points measured at Visit 4 (onset 15 minutes) and Visit 3B (duration 16 hrs.).

Study 12-100-0006 - Primary Efficacy Endpoint Results*

Timepoint (Minutes post-CAC)	Cetirizine 0.24% N=50	Vehicle N=50	Cetirizine 0.24% N=50	Vehicle N=50
	Visit 3B (Duration 8 Hrs.)		**Visit 4 (Onset 15 Mins.)**	
Ocular Itching ITT w/ LOCF [Mean Difference (*P*)]				
3	-0.93 (<0.0001)[1,2]		-1.38 (<0.0001)[1,2]	
5	-0.89 (<0.0001)[1,2]		-1.25 (<0.0001)[1,2]	
7	-0.99 (<0.0001)[1,2]		-1.10 (<0.0001)[1,2]	
Ocular Itching PP w/ OD [Mean Difference (*P*)]				
3	-0.93 (<0.0001)[1,2]			
5	-0.87 (<0.0001)[1,2]			
7	-0.98 (<0.0001)[1,2]			
Conjunctival Redness ITT w/ LOCF [Mean Difference (*P*)]				
7	-0.30 (0.0138)[1]		-0.33 (0.0001)[2]	
15	-0.03 (0.7660)[1]		-0.15 0.0518)[2]	
20	-0.01 (0.8790)[2]		-0.14 (0.1603)[1]	

* CAC data, based on either the two-sample t- test or the Wilcoxon rank sum test, whichever gave the better p-value comparing each of the cetirizine active groups to vehicle.
1 p value calculated using a two-sample t-test comparing each treatment group to vehicle.
2 p value calculated using a Wilcoxon rank sum test comparing each treatment group to vehicle.

Reviewer's comments: *For the ocular itching endpoint, cetirizine 0.24% showed statistical and clinical significance at all time points measured at Visit 4 (onset 15 minutes). At 8 hours, the product was still effective.*

For the conjunctival redness endpoint, cetirizine 0.24% failed to show statistical and clinical significance measured at Visit 4 (onset 15 minutes) and Visit 3B (duration 8hrs).

Study 13-100-0002 - Primary Efficacy Endpoint Results*

Timepoint (Minutes post-CAC)	Cetirizine 0.24% N=50	Vehicle N=48	Cetirizine 0.24% N=50	Vehicle N=48
	Visit 3B (Duration 8 Hrs.)		**Visit 4 (Onset 15 Mins.)**	
Ocular Itching ITT w/ LOCF [Mean Difference (*P*)]				
3	-0.92 (<0.0001)[1,2]		-1.53 (<0.0001)[1,2]	
5	-0.90 (<0.0001)[1,2]		-1.34 (<0.0001)[1,2]	
7	-0.84 (<0.0001)[1]		-1.07 (<0.0001)[1,2]	
Ocular Itching PP w/ OD [Mean Difference (*P*)]				
3	-1.07 (<0.0001)[1,2]			
5	-1.04 (<0.0001)[1,2]			
7	-0.94 (<0.0001)[1]			
Conjunctival Redness ITT w/ LOCF [Mean Difference (*P*)]				
7	-0.22 (0.1819)[1]		-0.03 (0.8299)[1]	
15	-0.06 (0.7118)[1]		0.09 0.5294)[1]	
20	-0.06 (0.7073)[1]		0.11 (0.4788)[1]	
Conjunctival Redness PP w/ OD [Mean Difference (*P*)]				

* CAC data, based on either the two-sample t- test or the Wilcoxon rank sum test, whichever gave the better p-value comparing each of the cetirizine active groups to vehicle.
1 p value calculated using a two-sample t-test comparing each treatment group to vehicle.
2 p value calculated using a Wilcoxon rank sum test comparing each treatment group to vehicle.

Reviewer's comments: *For the ocular itching endpoint, cetirizine 0.24% showed statistical and clinical significance at all time points measured at Visit 4 (onset 15 minutes). At 8 hours, the product was still effective.*

For the conjunctival redness endpoint, cetirizine 0.24% failed to show statistical and clinical significance at all time points measured at Visit 4 (onset 15 minutes) and Visit 3B (duration 8 hrs).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy variables for the three CAC studies: 11-100-0012, 12-100-0006, and 13-100-0002 included:

- Ciliary and Episcleral Redness: At Visits 3B and 4, the investigator separately assessed ciliary and episcleral redness with a slit lamp at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Chemosis: At Visits 3B and 4, the investigator assessed chemosis with a slit lamp at 7(±1), 15(±1) and 20(±1) minutes post-challenge.
- Eyelid Swelling: At Visits 3B and 4, subjects self-assessed eyelid swelling at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Tearing: At Visits 3B and 4, subjects self-assessed tearing at 7(±1), 15(±1), and 20(±1) minutes post-challenge.
- Individual Nasal Allergy Symptoms: At Visits 3B and 4, subjects self-assessed rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion at 7(±1), 15(±1) and 20(±1) minutes post-challenge.
- Composite Nasal Symptom Score: For Visits 3B and 4, binary composite scores for presence or absence of at least one nasal symptom were derived for the time points 7(±1), 15(±1), and 20(±1) minutes post-challenge by study statisticians using the individual nasal allergy symptom scores reported by each subject.

Reviewer's comments: *Statistically significant reduction was noted for the secondary efficacy variables of ciliary redness, episcleral redness, chemosis, eyelid swelling, tearing, individual nasal allergy symptoms (rhinorrhea, nasal pruritus, nasal congestion) and composite nasal symptom score at some or all post-challenge time points at Visits 3 and 4. Changes in ciliary redness and episcleral redness are not relevant for a product which fails to demonstrate clinical significance for conjunctival redness. The clinical relevance of the remaining secondary endpoints is not clear.*

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Refer to section 6.1.2.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In order to demonstrate clinical significance in a CAC study, the difference between groups should be at least one unit on a scale from 0-4 at a majority of the time points evaluated at the time of onset of the drug product's effect. This criterion for the endpoint of ocular itching was demonstrated in studies 11-100-0004, 11-100-0012, 12-100-0006, and 13-100-0002. A clinically significant duration of effect was not demonstrated at 16 or 24 hours in studies, 11-100-0004, or 11-100-0012, but aduration of 8 hours was marginally demonstrated in studies 12-100-0006, and 13-100-0002. A clinical effect on conjunctival redness was not demonstrated in any of the four studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As noted in section 6.1.8, the efficacy of the drug product has been demonstrated to remain at a clinically significant level for only 8 hours.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Primary Data Used To Evaluate Safety

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
11-100-0004 dose - response study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.05% 0.10% 0.24% Vehicle	1 drop OU @ Visits 3A, 4A and 5	6 weeks	Cetirizine 0.05%=25 0.10%=26 0.24%=25 Vehicle=25
11-100-0012 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visits 3A and 4 1 drop OU @ Visits3A and 4	Approx. 5 weeks	Cetirizine 0.24%=46 Vehicle=45
11-100-0013 safety and comfort study	Randomized, single-masked	Healthy adults	Formulation1:cetirizine 0.17% 0.24% Formulation2:cetirizine 0.24% Pataday Tears Naturale II	1 drop OD or OS 1 drop OD or OS 1 drop OD or OS Contralateral eye	1 day	Formulation1:cetirizine 0.17%=16 0.24%=1 Formulation2:cetirizine 0.24%=15 Pataday=14 Tears Naturale II =contralateral eye
12-100-0006 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visit 3A and Visit 4 1 drop OU @ Visit 3A and Visit 4	Approx. 5 weeks	Cetirizine 0.24%=50 Vehicle=50
13-100-0002 safety and efficacy study	Randomized, double-masked, vehicle controlled, CAC	History of allergic conjunctivitis	Cetirizine 0.24% Vehicle	1 drop OU @ Visit 3A and Visit 4 1 drop OU @ Visit 3A	Approx. 5 weeks	Cetirizine 0.24%=51 Vehicle=50

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
				and Visit 4		
14-100-0006 safety study	Randomized, double-masked, vehicle controlled	Subjects ≥ 2 yrs old with history or family history of atopic disease	Cetirizine 0.24% Vehicle	1 drop OU BID 1 drop OU BID	Approx. 6 weeks	Cetirizine 0.24%=341 Vehicle=171
14-100-0007 PK and safety study	Open-label	Healthy adults	Cetirizine 0.24%	1 drop OU BID for 1 week	Approx. 1 week	Cetirizine 0.24%=11

Reviewer's comments: *Adverse event rates were derived from adverse events pooled from the seven studies identified in the table above. These studies were pooled for safety evaluation because each study evaluated the 0.24% concentration of cetirizine, the proposed to-be-marketed dose strength.*

7.1.2 Categorization of Adverse Events

Routine clinical testing was used to establish the safety of topical ophthalmic drops (i.e., biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooled data across seven trials (Studies 11-100-0004, 11-100-0012, 11-100-0013, 12-100-0006, 13-100-0002, 14-100-0006, and 14-100-0007) was the primary data used to evaluate safety and in the analysis of common adverse events. Each of the seven trials evaluated the 0.24% concentration of cetirizine.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Mean Duration of Exposure in Individual Studies

Subject Duration of Exposure (Subject-Days)					
	Cetirizine 0.24% Final Formulation (N=514)	**Cetirizine 0.24% Other Formulation (N=40)**	**Total Cetirizine 0.24% (N=554)**	**Vehicle (N=341)**	**All Subjects (N=895)**
Study 11-100-0004					
N	0	25	25	25	50
Mean (SD)		21.7 (2.84)	21.7 (2.84)	23.0 (0.61)	22.4 (2.15)
Min, Max		14, 24	14, 24	22, 24	14, 24
Study 11-100-0012					
N	46	0	46	45	91
Mean (SD)	14.8 (3.02)		14.8 (3.02)	15.4 (0.61)	15.1 (2.19)
Min, Max	1, 16		1, 16	13, 16	1, 16
Study 11-100-0013					
N	15	15	30	0	30
Mean (SD)	1.0 (0.00)	1.0 (0.00)	1.0 (0.00)		1.0 (0.00)
Min, Max	1, 1	1, 1	1, 1		1, 1
Study 12-100-0006					
N	50	0	50	50	100
Mean (SD)	14.4 (2.05)		14.1 (2.05)	13.7 (3.32)	14.0 (2.77)
Min, Max	1, 16		1, 16	1, 16	1, 16
Study 13-100-0002					
N	51	0	51	50	101
Mean (SD)	12.8 (5.14)		12.8 (5.14)	13.3 (4.60)	13.1 (4.86)
Min, Max	1, 15		1, 15	1, 15	1, 15
Study 14-100-0006					
N	541	0	341	171	512
Mean (SD)	41.0 (6.27)		41.0 (6.27)	41.0 (6.20)	41.0 (6.24)
Min, Max	1, 48		1, 48	1, 45	1, 48
Study 14-100-0007					
N	11	0	11	0	11
Mean (SD)	7.4 (2.11)		7.4 (2.11)		7.4 (2.11)
Min, Max	1, 8		1, 8		1.8

Note: N in the headers represents the total number of subjects enrolled in each respective treatment group within the Safety population. Subjects participating in more than one trial are all included as independent subjects. Exposure is calculated as Date of Last Dose – Date of First Dose + 1, where Date of First Dose is assumed to be the Day 0 Date.

Reviewer's comments: *There is adequate exposure to assess the safety profile of cetirizine ophthalmic solution, 0.24%.*

7.2.2 Explorations for Dose Response

One dose-response study (Study 11-100-0004) was performed. Three concentrations of cetirizine (0.05%, 0.10%, and 0.24%) were evaluated. Cetirizine 0.24% was the more effective concentration in reducing ocular itching with a duration of effect approximately 8 hours. Cetirizine 0.24% was selected for development.

See Section 5.3 for more details of the dose-response study.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

The routine clinical testing used to evaluate the safety concerns of topical ophthalmic drops (i.e., biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the clinical trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable. This data was not collected.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. Common side effects include for this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, taste perversion/bitter taste. There was adequate AE evaluation for this product.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the clinical trial.

7.3.2 Nonfatal Serious Adverse Events

One (0.2%) subject in the cetirizine group and 1 (0.3%) subject in the vehicle group reported a serious adverse event (SAE.) One of the subjects with an SAE withdrew from the study; however, the other subject completed the study.

Serious Adverse Events

Study Number	Subject Number	Treatment	System Organ Class/Preferred Term	Ocular/Non-ocular	Severity
14-100-0006	1054	Cetirizine 0.24%	Infections and Infestations/Herpes zoster	Non-ocular	Severe
14-100-0006	3020	Vehicle	Immune system disorders/Anaphylactic shock	Non-ocular	Severe

7.3.3 Dropouts and/or Discontinuations

Subject Withdrawals Due to Adverse Events

Study Number	Subject Number	Treatment	System Organ Class/Preferred Term	Ocular/Non-ocular	Severity
11-100-0004	001-1058	Cetirizine 0.24%	Respiratory, Thoracic and Mediastinal Disorders/Epistaxis	Non-ocular	Moderate
12-100-0006	001-1144	Cetirizine 0.24%	Respiratory, Thoracic and Mediastinal Disorders/Pharyngeal Oedema	Non-ocular	Moderate
12-100-0006	001-1016	Vehicle	Eye Disorders/ Punctate Keratitis	Ocular	Moderate
14-100-0006	1062	Cetirizine 0.24%	Infections and Infestations/ Conjunctivitis viral	Ocular	Moderate
14-100-0006	1077	Vehicle	Eye Disorder/ Eye discharge Eye Disorder/ Ocular Hyperaemia Musculoskeletal and Connective Tissue Disorder/ Pain in jaw General Disorders and Administration Site Conditions/ Instillation site pain	Ocular Ocular Non-ocular Ocular	Moderate Moderate Moderate Mild
14-100-0006	1102	Vehicle	Nervous System disorders/ Headache	Non-ocular	Moderate
14-100-0006	1124	Cetirizine 0.24%	Infections and Infestations/ Gastroenteritis viral	Non-ocular	Moderate
14-100-0006	3020	Vehicle	Immune system disorders/ Anaphylactic shock	Non-ocular	Severe
14-100-0006	3035	Vehicle	Pregnancy, Puerperium, and Perinatal conditions/ Pregnancy	Non-ocular	Mild

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Incidence ≥ 1 % Treatment-Emergent[a] Adverse Events (TEAE) by Preferred Term and Treatment

System Organ Class (SOC) Preferred Term (PT)	**Cetirizine 0.24% Final Formulation (N=511)**	**Cetirizine 0.24% 'Other' Formulation (N=40)**	**Total Cetirizine 0.24% (N=551)**	**Vehicle (N=329)**	**All Subjects (N=880)**
OCULAR	N (%)	N (%)	N (%)	N (%)	N (%)
Eye Disorders					
Conjunctival hyperemia	27 (5.3)	0 (0.0)	27 (4.9)	19 (5.8)	46 (5.2)
Ocular hyperemia	10 (2.0)	0 (0.0)	10 (1.8)	3 (0.9)	13 (1.5)
Visual acuity reduced	3 (0.6)	0 (0.0)	3 (0.5)	7 (2.1)	10 (1.1)
General Disorders and Administration Site Conditions					
Instillation site pain	20 (3.9)	0 (0.0)	20 (3.6)	3 (0.9)	23 (2.6)

Reviewer's comments: *The most ocular common adverse events were conjunctival hyperemia (5%), instillation site pain (4%), and ocular hyperemia (2%). In the proposed labeling, ocular hyperemia and conjunctival hyperemia are combined into one term – hyperemia. All non-ocular adverse events occurred in <1% of subjects in both treatment groups.*

7.4.2 Laboratory Findings

No clinically relevant laboratory abnormalities were detected in any of the trials that conducted laboratory evaluation.

7.4.3 Vital Signs

No clinically significant changes from baseline for vital sign parameters were seen.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed.

7.4.5 Special Safety Studies/Clinical Trials

The safety trial (Study 14-100-0006) enrolled 59 pediatric subjects age ≥2 years to ≤ 10 years. Cetirizine ophthalmic solution, 0.24% was found to be safe and well-tolerated in the pediatric population 2-10 years of age with no unexpected safety issues in any pediatric subject. Five (5) TEAEs were reported in the pediatric population. One TEAE (conjunctival hyperemia) occurred in 1 subject (1.7%) in the vehicle treatment group. The other 4 TEAEs were non-ocular and occurred in 4 subjects (6.8%), 3 of the TEAEs (2 events of otitis media and 1 event of hand foot and mouth disease) were reported by subjects in the cetirizine group and 1 TEAE (sunburn) was reported by a subject in the vehicle group. No pediatric subject discontinued from the study due to a TEAE.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not observed.

7.5.2 Time Dependency for Adverse Events

There were no time dependent adverse events noted.

7.5.3 Drug-Demographic Interactions

The demographics in the safety population included subjects from age 2 and older. There were no significant differences between cetirizine ophthalmic solution 0.24% and the vehicle group with regards to age, gender, ethnicity, eye color or race.

7.5.4 Drug-Disease Interactions

A review of adverse events revealed no untoward safety issues in each of the subpopulations categorized by concomitant diseases.

7.5.5 Drug-Drug Interactions

No investigations on potential drug-drug interactions were performed. During the clinical development of cetirizine, no drug-drug interactions were reported.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of cetirizine ophthalmic solution 0.24%, a topical ocular preparation, no human carcinogenicity studies were conducted.

In a 2-year carcinogenicity study in rats, orally administered cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 550 times the MRHOD on a mg/m^2 basis).

In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 550 times the MRHOD on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 55 times the MRHOD, on a mg/m^2 basis). The clinical significance of these findings is not known.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category B. Reproduction studies have been performed in mice, rats and rabbits at doses of up to approximately 1300, 4930 and 7400 times the maximum recommended human ophthalmic dose (MRHOD) on a mg/m^2 basis, respectively and have revealed no evidence of harm to the fetus due to cetirizine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of cetirizine ophthalmic solution, 0.24% in nursing mothers is not recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug was tested in a pediatric population. Safety and efficacy of cetirizine ophthalmic solution have not been established in pediatric patients less than 2 years of age because the diagnosis of allergic conjunctivitis cannot be reliably made in patients of this age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in patients greater than 10 years of age because there are no differences in the clinical characteristics or course of the disease at any age.

The Agency issued a Written Request for Cetirizine Ophthalmic Solution, 0.24% on September 15, 2015. The Written Request identified the need for pediatric safety information specific to Cetirizine Ophthalmic Solution, 0.24% and included the Agency's agreement with the protocol and statistical analysis plan for Study 14-100-0006, a double masked, randomized, vehicle-controlled, parallel-group study evaluating the safety of Cetirizine Ophthalmic Solution, 0.24% in adults and pediatric patients 2 to 17 years of age. The Agency amended the Written Request on March 29, 2016. According to the Amended Written Request, the report for Study 14-100-0006 was to be submitted to the Agency on or before July 31, 2016. The report for Study

14-100-0006 is included in this application. Prior to this application, Nicox Ophthalmics, Inc. (Nicox) had not submitted this report to the Agency.

This application was placed on the schedule of the Pediatric Exclusivity Board for August 23, 2016. The Board granted exclusivity on 8/29/16.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no anticipated abuse potential for this product. No withdrawal or rebound effects are anticipated.

7.7 Additional Submissions / Safety Issues

The 120 Day Safety Update was received on August 8, 2016. The submission reported that since the NDA filing, Applicant has initiated an additional clinical safety trial (Study 15-100-0010) to evaluate the safety of cetirizine ophthalmic solution 0.24% dosed three times a day (TID) in adults and pediatric subjects. Except for the dosing regimen, the study design is identical to safety Study 14-100-006 BID dosing). Study 15-100-0010 is ongoing. Interim safety results through June 30, 2016 were included in the submission. The information contained in the safety update is comparable to the information reviewed for the original NDA. No edits to the labeling were proposed by the applicant based on the 120 Day Safety Update.

8 Postmarket Experience

Cetirizine ophthalmic solution 0.24% is not marketed in any country.

9 Appendices

9.1 Literature Review References

There was no additional relevant material identified from the literature for this application.

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached appendix.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held. No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

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/s/

LUCIOUS LIM
09/26/2016

WILLIAM M BOYD
09/26/2016