# A Multi-Center, Randomized, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Efficacy and Safety of OTX-DP for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

**Investigational Protocol CLN-Protocol-0052**

**Revision 002**
**29-October-2019**

**Sponsor:**
**Ocular Therapeutix, Inc.**
**15 Crosby Drive**
**Bedford, MA 01730**

**A Multi-Center, Randomized, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Efficacy and Safety of OTX-DP for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)**

I hereby agree to participate in the clinical investigation of **OTX-DP** sponsored by Ocular Therapeutix, Inc. (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with the agreement, the investigational plan, and applicable regulations. I agree to protect the rights, safety, and welfare of subjects under my care; I agree to adhere to the guidelines outlined in 21 CFR Part 312, other applicable United States Food and Drug Administration (FDA) regulations, and conditions of approval imposed by the reviewing IRB and the FDA. I agree to supervise all uses of the intracanalicular insert and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the FDA to verify compliance with applicable federal regulations related to clinical research on human subjects.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify the Study Sponsor 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

Any data generated as a result of this investigation will be the exclusive property of the Study Sponsor who retains all rights of publication. I understand that the Study Sponsor encourages me to pursue independent publications related to my experience with this intracanalicular insert with the understanding that the Study Sponsor reserves the right of prior review and approval of these publications.

I agree to provide to the Study Sponsor my current curriculum vitae (CV) along with the current CV of those physicians at this institution who will be using this insert or participating in this study as Sub-investigators under my supervision. These CVs include education, training, and the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of a Study Sponsor, and IRB/IEC or the FDA.

I understand that this investigation, protocol and results are confidential, and I agree not to disclose any such information to any person other than a representative of Study Sponsor without the prior written consent of the Study Sponsor.

**Accepted by:**

| Principal Investigator Signature | Date | Printed Name |
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## PROTOCOL REVISION HISTORY

| Date | Revision | Description of Modifications | Rationale for Modification |
|---|---|---|---|
| 26-March-2019 | 001 | Original Issue | N/A |
| 29-OCT-2019 | 002 | Removed requirement for punctum size between 0.4 mm and 0.9mm (formerly exclusion criterion #17) | Now that the product is available commercially, Ocular has experience placing the insert in various sizes. The dilated punctum size is the relevant criterion for study entry |
| | | Defined the standard for re-screening subjects | To clarify that subjects who meet the current eligibility criteria can be re-screened |
| | | Stated when to capture slit lamp findings in Medical History | To remain consistent with the definition of an adverse event |
| | | Clarified example of laboratory adverse event | To remain consistent with the definition of an adverse event |
| | | Fixed minor typos and inconsistencies | Correction of minor clerical errors |

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# 1. ABBREVIATIONS

| Abbreviation | Meaning |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| API | Active pharmaceutical ingredient |
| BCVA | Best corrected visual acuity |
| BOCF | Baseline Observation Carried Forward |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| eCRF | electronic Case report form |
| CV | Curriculum vitae |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FDA | Food and Drug Administration |
| GC | Glucocorticoid |
| GCP | Good Clinical Practice |
| HIPAA | Health Information Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IOL | Intraocular Lens |
| IOP | Intraocular pressure |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ITT | Intent To Treat |
| LASIK | laser in situ keratomileusis |
| LOCF | Last Observation Carried Forward |
| logMAR | logarithm of the minimum angle of resolution |
| LS | Least Square |
| MCMC | Markov Chain Monte Carlo |
| mmHg | Millimeters of Mercury |
| NCS | Not clinically significant |
| NSAID | Nonsteroidal anti-inflammatory drug |
| PEG | Polyethylene glycol |
| PP | Per Protocol |
| OD | Right eye |
| Ora-CAC® | Conjunctival allergen challenge |
| OS | Left eye |
| OTC | Over the counter |
| OU | Both eyes |
| PV | Placebo Vehicle |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| US | United States |
| WCO | Worst Case Observation |

# 2. SYNOPSIS

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| **Study Title** | A Multi-Center, Randomized, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Efficacy and Safety of OTX-DP for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®) |
| **Investigational Product** | OTX-DP (dexamethasone ophthalmic insert, 0.4mg) or PV (Placebo Vehicle) |
| **Phase of Clinical Study** | Phase 3 |
| **Number of Sites** | Approximately 4 investigative sites in the United States |
| **Study Objective** | To evaluate the efficacy and safety of OTX-DP as a dexamethasone ophthalmic insert when placed in the canaliculus of the eyelid for the treatment of the signs and symptoms of allergic conjunctivitis. |
| **Product Description** | OTX-DP is a resorbable hydrogel intracanalicular insert containing an anti-inflammatory glucocorticoid agonist. The insert is designed to be placed into the punctum and is retained in the canaliculus for the entire drug delivery duration. Over time, the insert softens and liquefies via hydrolysis, resulting in clearance through the nasolacrimal duct.<br><br>Each OTX-DP ophthalmic insert contains 0.4mg dexamethasone and a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein. The fluorescent PEG allows the insert to be visualized by the physician utilizing a blue light source and yellow filter.<br><br>The Placebo Vehicle (PV) is the same fluorescent PEG hydrogel insert as OTX-DP, except that it does not contain dexamethasone. |
| **Number of Subjects Planned** | Approximately 80 subjects will be enrolled into this clinical trial. Approximately 10 additional subjects will be enrolled to make up for any subjects who did not complete Visit 6b CAC procedures. |
| **Study Population** | Subjects of at least 18 years of age of either sex and of any race who meet all of the inclusion criteria and none of the exclusion criteria. |
| **Study Design and Overview** | This is a prospective, multi-center, randomized, double-masked, vehicle-controlled study to evaluate the efficacy and safety of OTX- DP compared to PV for the treatment of the signs and symptoms of allergic conjunctivitis.<br><br>The modified Ora-CAC® model used in the current study has been developed to study the interactions between the early and late phases of the allergic response in the eye, and to evaluate the effects of pharmaceutical intervention. The modified CAC model utilizes 3 challenges conducted over a 2-day interval to evaluate the effectiveness of a test agent to: 1) prevent an acute ocular allergic reaction (the initial CAC), and 2) evaluate the test agent's ability to prevent an acute ocular allergic reaction in the presence of subclinical late phase inflammation (the latter re-challenge CACs).<br><br>The modified CAC model provides the opportunity to investigate the |

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| | effects of the underlying inflammatory reaction on the ability of the tissues to mount a robust acute response to a subsequent allergen challenge. The modified CAC model also provides a means to investigate the mechanism(s) of action of anti-inflammatory agents in the treatment of allergic reactions.<br><br>This study consists of 13 office visits over a period of approximately 5 to 11 weeks.<br><br>Qualifying subjects will be randomized 1:1 at Visit 4b (Day 1) to receive one of the following treatment arms bilaterally:<br><br>• OTX-DP (N=40 subjects) or<br>• PV (N=40 subjects)<br><br>In the OTX-DP arm, subjects will receive bilateral OTX-DP (dexamethasone ophthalmic insert, 0.4mg) inserts.<br><br>Randomization is at a 1:1 ratio (active:vehicle) |
| **Summary of Visit Schedule** | • Visit 1 (Day -45 to Day -6): Screening Visit<br>• Visit 2 (Day -5+1 day): CAC screening / titration<br>• Visit 3a (Day -4+1 day): CAC confirmation #1<br>• Visit 3b (Day -4+1 day; 8 hours post V3a): CAC confirmation #2<br>• Visit 4a (Day -3 +1 day; 24±6 hours post V3a): CAC confirmation #3<br><br>***Subjects will be asked to return to the office 2-3 days from the time of their Baseline CAC (Visit 4a) for IP Insertion (Visit 4b/Day 1)***<br><br>• Visit 4b (Day 1): Enrollment/Randomization/Insertion of OTX- DP or PV<br><br>• Visit 5 (Day 7; 6 days post-insertion) CAC #1<br>• Visit 6a (Day 8; 7 days post-insertion) CAC re-challenge #2<br>• Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) CAC re-challenge #3<br><br>***The Visit 6b (Day 8) measures OTX-DP efficacy 7 days post-insertion.***<br><br>• Visit 7 (Day 14; 13 days post-insertion) CAC re-challenge #1<br>• Visit 8a (Day 15; 14 days post-insertion) CAC re-challenge #2 Visit 8b (Day 15; 14 days post-insertion; 8 hours from Visit 8a) CAC re-challenge #3<br>• Visit 9 (Day 30+3): Study Exit |
| **Primary Efficacy Evaluations** | The primary endpoint is:<br>Ocular itching evaluated by the subject on Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) |

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| **Secondary Efficacy Evaluations** | Key secondary outcomes are the measures of ocular itching at the following visits at 3(±1), 5(±1), and 7(±1) minutes post-CAC:<br>• Visit 6a (Day 8; 7 days post-insertion)<br>• Visit 5 (Day 7; 6 days post-insertion)<br>• Visit 8b (Day 15; 14 days post-insertion; 8 hours from Visit 8a)<br>• Visit 8a (Day 15; 14 days post-insertion)<br>• Visit 7 (Day 14; 13 days post-insertion)<br><br>Other secondary efficacy measures are ocular itching at Visits 5, 6a, 6b, 7, 8a, and 8b at the 10(±1) minutes post-CAC and the following assessments made at Visits 5, 6a, 6b, 7, 8a, and 8b at 7(±1), 15(±1), and 20(±3) minutes post-CAC:<br>• Conjunctival redness evaluated by the investigator (0-4 scale, allowing half unit increments)<br>• Ciliary and episcleral redness evaluated by the investigator (0-4 scale, allowing half unit increments)<br>• Chemosis evaluated by the investigator (0-4 scale, allowing half unit increments)<br>• Eyelid swelling evaluated by the subject (0-3 scale, NOT allowing half unit increments)<br>• Tearing/watery eyes evaluated by the subject (0-4 scale, NOT allowing half unit increments)<br>• Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0-4 scale, NOT allowing half-unit increments)<br>Nasal symptom composite score based on the assessments of rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion (analyzed as a qualitative measure determined as the presence or absence of at least one nasal symptom [present/absent], and as a quantitative measure calculated as the sum of the four component symptom scores [ranging from 0 to 16]) |
| **Safety Evaluations** | • Adverse Events (AEs) (reported, elicited, and observed)<br>• Best Corrected Visual Acuity (BCVA) using an ETDRS chart<br>• Slit-lamp biomicroscopy, including punctum exam<br>• Intraocular Pressure (IOP)<br>• Dilated Fundoscopy Examination |
| **Inclusion Criteria** | *Each subject must:*<br>1. be at least 18 years of age of either sex and any race;<br>2. provide written informed consent and sign the HIPAA form;<br>3. be willing and able to follow all instructions and attend all study visits;<br>4. be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6 in Section 5.5.3)<br>5. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study period;<br>6. have a BCVA of greater than or equal to 50 ETDRS letters (20/100 Snellen equivalent or better) in each eye as measured at Visit 1;<br>7. agree to have urine pregnancy testing (for women considered capable |

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| | of becoming pregnant, including 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]) performed at Visit 2 and at the exit visit; not be lactating; and agree to use a medically acceptable form of birth control throughout the clinical study duration;<br>8. have a positive history of ocular allergies and a positive skin test reaction to a perennial allergen (cat dander, dog dander, dust mites, cockroaches) and a seasonal allergen (trees, grasses, and/or ragweed) as confirmed by the allergic skin test conducted at Visit 1 or given to the subject within 24 months of the subject's Visit 2;<br>9. have a positive bilateral CAC reaction (defined as ≥ 2 itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;<br>10. have an average of ≥ 3 itching and ≥2.5 conjunctival redness for both eyes after the first three post-CAC assessment time points at Visit 4a |
| **Exclusion Criteria** | *Each subject must not:*<br>1) have known contraindications or sensitivities to the use of any of the medications required by the protocol;<br>2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or study parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);<br>3) have had a history of refractive surgery (including LASIK procedures) within the past 2 years;<br>4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;<br>5) have the presence of an active ocular infection (bacterial, viral or fungal), a current diagnosis or history of Herpes Simplex Keratitis, or a positive history of an ocular herpetic infection at any visit;<br>6) use any of the following disallowed medications* during the period indicated **prior to Visit 2** and during the study:<br>**7 Days**<br>• systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer drug combinations, H1 antihistamine- vasoconstrictor drug combinations;<br>• decongestants;<br>• monoamine oxidase inhibitors;<br>• all other topical ophthalmic preparations (including artificial tears);<br>• lid scrubs;<br>• prostaglandins or prostaglandin derivatives;<br>• ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);<br>**Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 2 and will continue to be maintained for the duration of the study.*<br>**14 Days**<br>• inhaled, ocular or topical corticosteroids or mast cell stabilizers; |

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| | **45 Days**<br>• depot-corticosteroids;<br>**2 months**<br>• 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 study)<br>7) have a congenital or ocular anomaly (including punctal or lid ectropion, entropion, trichiasis, or supernumerary puncta) or anomalies of the punctum (including lack of good punctal apposition in both eyes);<br>8) have a diagnosis of any significant uncontrolled illness;<br>9) history of alcohol or drug abuse in the past year;<br>10) known history of moderate to severe allergic asthmatic reactions to any of the study allergens;<br>11) have planned surgery (ocular or systemic) during the trial period or within 30 days after;<br>12) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;<br>13) be a female who is currently pregnant, planning a pregnancy, or lactating;<br>14) have a score of >0 for ocular itching and/or >1 for conjunctival redness prior to the challenge in either eye at Visit 2;<br>15) have an intraocular pressure that is less than 5 mmHg or greater than 22 mmHg or any type of glaucoma at Visit 2;<br>16) have had a history of an IOP increase as a result of steroid treatment;<br>17) have an unsuccessful transient punctum dilation to 0.7 mm prior to insertion of OTX-DP or PV;<br>18) be an employee of the site that is directly involved in the management, administration, or support of the study, or are an immediate family member of the same. |
| **General Statistical Methods and Types of Analysis** | In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages.<br><br>Efficacy analyses will be conducted on the intent-to-treat (ITT) population using multiple imputation using Markov Chain Monte Carlo (MCMC) for missing and incomplete efficacy data. The ITT population is defined as all randomized subjects. All data will be included in the ITT population and will be analyzed as randomized. The average of each subject's eyes at each time point within each visit will be used for efficacy analyses.<br><br>Sensitivity analysis on the primary endpoint will be performed on the Per-Protocol (PP) population defined as all subjects who complete the study through Visit 6b (Day 8) without major protocol violations. The PP population will be analyzed as treated using observed data only.<br><br>Safety analyses will be conducted on the safety population defined as all |

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| | randomized subjects who received the IP. The safety population will be analyzed as treated.<br><br>**Sample Size:**<br>Approximately 80 subjects will be randomized at Visit 4b in a 1:1 ratio across the two treatment arms (40 OTX-DP; 40 PV). Up to approximately 10 additional subjects may be enrolled to make up for any subjects who did not complete Visit 6b CAC procedures.<br><br>A total of 40 subjects in each treatment arm will provide 97.0%, 99.8%, and 99.9% power to demonstrate a statistically significant difference in ocular itching between OTX-DP and PV treated subjects at each of the 3, 5, and 7 minute post-CAC time points of Visit 6b, respectively, assuming a treatment difference of 0.87 units 3 minutes post-CAC, 1.08 units at 5 minutes post-CAC, and 1.13 units at 7 minutes post-CAC; a standard deviation of 1.0 unit at all time points; and a two-sided Type I error of 0.05.<br><br>Assuming independence between time points, 40 subjects per group will have at least 96.7% power to demonstrate a statistically significant difference over all post-CAC time points at Visit 6b for ocular itching between OTX-DP and PV treated subjects.<br>Additionally, 40 subjects in each treatment arm will have at least 55.9% probability of showing a point estimate treatment difference for ocular itching between OTX-DP and PV treated subjects of at least 1.0 unit for a majority of the post-CAC time points and 0.5 units for all of the post-CAC time points at Visit 6b, using the same assumptions previously stated.<br><br>**Primary Hypothesis:**<br>Statistical hypotheses for the primary efficacy endpoint of ocular itching at Visit 6b are as follows:<br><br>$H_{10}$: There is no difference in mean ocular itching scores between OTX-DP and PV treated subjects for at least 1 of the 3 time points during Visit 6b.<br><br>$H_{1a}$: There is a difference in mean ocular itching scores between OTX-DP and PV treated subjects for all 3 time points during Visit 6b.<br><br>**Primary and Key Secondary Analyses:**<br>The primary efficacy variable is ocular itching measured at Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) measured at 3(±1), 5(±1), and 7(±1) minutes post-CAC.<br><br>The key secondary variables are ocular itching measured at Visit 5 (Day 7; 6 days post-insertion), Visit 6a (Day 8; 7 days post- insertion), Visit 7 (Day 14; 13 days post-insertion), Visit 8a (Day 15; 14 days post-insertion), and Visit 8b (Day 15; 14 days post- insertion; 8 hours from Visit 8a) measured at 3(±1), 5(±1), and 7(±1) minutes post-CAC. The |

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| | average of each subject's eyes at each post-CAC time point will be used as the unit of analysis. The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population with multiple imputation using Markov Chain Monte Carlo (MCMC) for missing data.<br><br>Analysis of covariance (ANCOVA) models will be run at each post- CAC time point of a given visit to estimate least square (LS) treatment means. These models will include the time appropriate post-CAC® scores at Visit 4a as a baseline covariate for adjustment and treatment group as the sole factor. LS means will be used to make treatment comparisons. Statistical significance of treatment differences will be determined using a two-sided significance level of $\alpha = 0.05$.<br><br>Two-sample t-tests will be used as unadjusted sensitivity analyses at each post-CAC time point, as well as non-parametric Wilcoxon rank sum tests. Sensitivity analyses will be conducted on the ITT population with last observation carried forward (LOCF), worst case observation (WCO), and baseline observation carried forward (BOCF) for missing data, as well as using observed data only for the ITT and PP populations.<br><br>**Other Secondary Analyses:**<br>The remaining secondary variables including ocular itching (at later time points), conjunctival, episcleral, and ciliary redness; eyelid swelling; tearing/watery eyes; rhinorrhea; nasal pruritus; ear or palate pruritus; and nasal congestion will be analyzed in a manner similar to the primary and key secondary variables using ANCOVA models by time point. The secondary analyses will be conducted using observed data only on the ITT and PP populations. |

# 3. PRINCIPAL CONTACTS

Please refer to Study Contact List.

# 4. INTRODUCTION

## 4.1. Background and Rationale

Ocular Therapeutix, Inc. is a biopharmaceutical company specifically focused on developing novel delivery systems for therapeutic products in order to address unmet and/or underserved medical needs. Ocular Therapeutix was founded to further develop its proprietary polyethylene glycol (PEG) hydrogel technology in various applications. Ocular Therapeutix has developed a resorbable intracanalicular hydrogel insert that serves as the platform for multiple drug delivery products and is being developed to deliver various APIs that are already approved by the Food and Drug Administration (FDA). The insert is designed to be placed into the punctum and is retained in the canaliculus for the intended drug delivery duration. Over time, the insert softens and liquefies via hydrolysis, resulting in clearance through the nasolacrimal duct. One of these inserts, known commercially as DEXTENZA®, a dexamethasone ophthalmic insert (OTX-DP) was approved by the FDA on November 30, 2018 for the treatment of pain following ophthalmic surgery.

Based on its design, OTX-DP provides potential benefits in that it requires only a single application by the physician, thereby eliminating the potential for patient non-compliance and also provides consistent delivery of medication to the ocular surface over the intended duration of treatment. In addition, the fluorescent PEG hydrogel allows for physician and subject visualization of OTX-DP. Further, the drug inserts do not contain antimicrobial preservatives, thus providing an additional safety benefit.

## 4.2. Prior Experience with OTX-DP Inserts

Glucocorticoids (GCs) are among the most effective and widely prescribed therapies in the treatment of acute and chronic inflammatory diseases, including ocular inflammation, and are particularly effective in treating later phase ocular conjunctivitis reactions (Choi et al, 2008). GCs such as dexamethasone do not affect immune cell membranes or histamine release mechanisms (Leonardi et al, 2012). They are, however, potent and efficacious anti-inflammatory agents which exert their therapeutic effects by binding to the glucocorticoid receptor leading to modulation of gene expression through down regulation of transcriptional regulators (Rhen et all, 2005). They may also modulate the mast cell response by inhibiting cytokine production, recruitment, and activation of inflammatory cells (Rhen et all, 2005). As a consequence of their anti-inflammatory properties, ophthalmic steroids are commonly used in the treatment of acute ocular conditions such as conjunctivitis, uveitis, allergy, dry eye, diabetic macular edema, and postoperative inflammation in cataract patients. Administration of these anti-inflammatory agents has been shown to decrease allergic signs and symptoms, not only at 5-6 hours post challenge, but also at shorter times generally considered to represent an acute response time frame (Leonardi et al, 2002). In fact, one study suggests that treatment with a low-dose steroid (desonide) can inhibit or attenuate the allergic reaction phase that initiates the transition from early acute to the chronic inflammatory response (Leonardi et al, 2002). Consequently, when mast-cell stabilizers and antihistamines fail to control the allergic response, less potent topical ophthalmic GCs such as loteprednol, rimexolone, and fluorometholone are used first, with dexamethasone prescribed later, at the lowest dose and for the shortest duration of time, in cases that are severe and/or unresponsive to other forms of treatment (Rizzo et al, 2006).

Use of GCs can be limited, however, by their potential (especially after long-term systemic treatment)

to induce a number of severe and sometimes irreversible side effects, such as osteoporosis, diabetes, Cushing's syndrome, glaucoma, and muscle wasting (Schäcke et al, 2002, Rizzo et al, 2006). For local ocular administration, GCs exhibit a variety of effect/side effect rations, with the primary adverse events (AEs) of concern being elevation of intraocular pressure (IOP), cataract formation, and increased vulnerability to superinfection (Wang et al, 2009, Kersey et al, 2006, Rizzo et al, 2006). All currently marketed ophthalmic steroids carry the warning that use for longer than 14 days should only be carried out under close physician supervision, and it is generally recommended that the dose be tapered slowly over several days (Rizzo et al, 2006).

Dexamethasone, one of the most powerful GCs, is already marketed in the US as a sterile ophthalmic solution for the treatment of "steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis…". While dexamethasone and other GCs are presumed to be the most clinically effective in the treatment of late-phase inflammatory allergic reactions, their well known safety limitations for long-term use prohibit wide-spread adoption of this treatment.

Use of the OTX-DP seasonally creates a low, tapered, consistent dose of dexamethasone, possibly minimizing or possibly eliminating negative side effects of general topical ophthalmic GC use, while retaining its anti-inflammatory effects that may be particularly beneficial in the treatment of late-phase ocular allergy.

One Phase 2, multicenter, prospective, randomized, double-masked vehicle controlled study in 68 subjects was completed utilizing the modified Ora-CAC® model. The study evaluated the safety and efficacy of OTX-DP as a sustained release drug depot for the treatment of the signs and symptoms of chronic allergic conjunctivitis. At 2 weeks, 4 weeks and 6 weeks after insertion of the OTX-DP, subjects underwent a series of 4 CACs over a period of 48 hours followed by clinical evaluation of the signs and symptoms of chronic allergic conjunctivitis. The co-primary efficacy endpoints were ocular itching and conjunctival redness at 14 days after
OTX-DP insertion. OTX-DP was shown to be efficacious. OTX-DP treated subjects had significantly lower ocular itching and conjunctival redness scores at all time points following repeated challenge at 14 days post insertion. The effect was long lasting with a duration of action of at least 6 weeks following plug insertion. The majority of adverse events (AEs) were mild, and evenly distributed between the OTX-DP group (14 AEs in 11 subjects) and the vehicle group (12 AEs in 10 subjects).

A Phase 3, multicenter, prospective, randomized, double-masked vehicle controlled study in 72 subjects was completed utilizing the modified Ora-CAC® model. The study evaluated the safety and efficacy of OTX-DP as a sustained release drug depot for the treatment of the signs and symptoms of chronic allergic conjunctivitis. At 1, 2 and 4 weeks after insertion of the OTX-DP, subjects underwent a series of 4 CACs over a period of 48 hours followed by clinical evaluation of the signs and symptoms of chronic allergic conjunctivitis. The primary efficacy endpoints were ocular itching and conjunctival redness at 7 days after OTX-DP insertion. OTX-DP was shown to be efficacious. OTX-DP treated subjects had lower conjunctival redness and significantly lower ocular itching scores at all time points following repeated challenge at 7 days post insertion. The effect was long lasting with a duration of action of at least 4 weeks following plug insertion. The majority of adverse events (AEs) were mild or moderate, and evenly distributed between the OTX-DP group (4 AEs in 3 subjects) and the vehicle group (7 AEs in 4 subjects).

A second Phase 3, multicenter, randomized, double-masked, vehicle controlled study in 83 subjects was completed utilizing the modified Ora-CAC® model. The study evaluated the safety and efficacy of OTX-DP as a sustained release drug depot for the treatment of the signs and symptoms of chronic allergic conjunctivitis. At 1, 2 and 4 weeks after insertion of the OTX-DP, subjects underwent a series

of 4 CACs over a period of 48 hours followed by clinical evaluation of the signs and symptoms of chronic allergic conjunctivitis. The primary efficacy endpoint was ocular itching at 7 days after OTX-DP insertion. OTX-DP was not shown to be efficacious as treatment group differences were not statistically significant at the Day 7 primary endpoint. Six subjects in the OTX-DP group experienced seven AEs and 11 subjects in the PV group experienced a total of 17 AEs.

OTX-DP is designed to overcome potential patient non-compliance due to the repeated dosing regimens associated with topical ophthalmic solutions, and to improve the delivery such that the drug level is maintained over the treatment period. The efficacy and safety of OTX-DP compared to PV for the treatment of ocular inflammation and pain in subjects undergoing cataract surgery with implantation of an intraocular lens (IOL) have been recently evaluated in three Phase 3 studies involving 541 OTX-DP treated subjects. The most common ocular adverse reactions that occurred in patients treated with OTX-DP were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); and corneal edema (1%).The most common non-ocular adverse reaction that occurred in patients treated with OTX-DP was headache (1%).

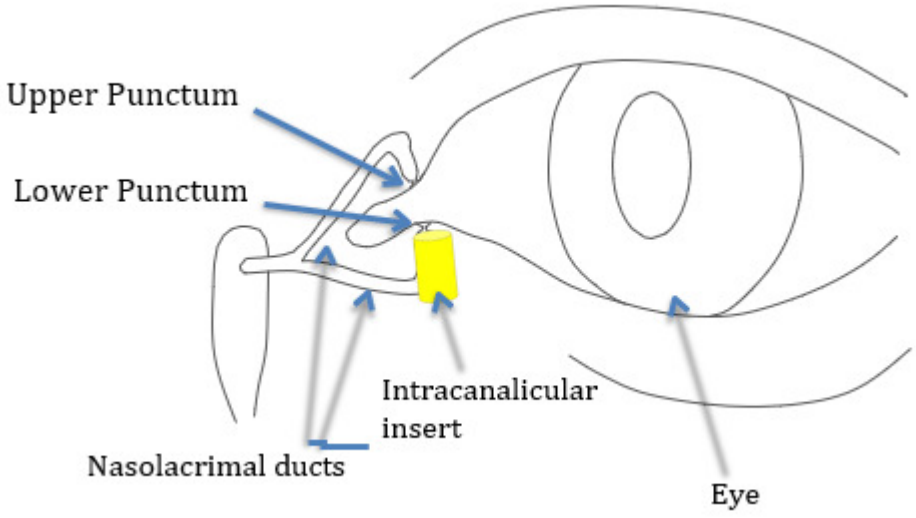
## 4.3. Description of Treatment

OTX-DP (dexamethasone ophthalmic insert, 0.4mg) is a resorbable hydrogel intracanalicular insert consisting of two main components: dexamethasone and a polyethylene glycol (PEG)- based hydrogel conjugated with fluorescein.

The hydrogel intracanalicular insert is designed to be placed in the canaliculus and swell on contact with moisture to occlude the lumen, securing it in place. Once the OTX-DP or PV swells to fill the canaliculus, it is designed to hydrolyze and be resorbed.

OTX-DP or PV is provided to the Investigator as a terminally-sterilized dried product. The product is packaged in a hermetically sealed foil pouch to maintain stability and sterility over time. It is placed into the punctum (Figure 1) by the Investigator using forceps. The instructions for the insertion procedure are described in Appendix G.

**Figure 1 Placement of Intracanalicular Insert in the Canaliculus**



### 4.3.1. Placebo Vehicle

The control, PV, is the same fluorescent PEG hydrogel as OTX-DP, except that it does not contain drug.

### 4.3.2. Safety of OTX-DP

Additional details as to the physical, chemical and pharmaceutical properties and product description are provided in the Investigator's Brochure (IB). Packaging configuration is also provided in the IB.

## 4.4. Intended Indication

OTX-DP is being studied for the intended use in the treatment of ocular itching associated with allergic conjunctivitis.

## 4.5. Risk/Benefits

The potential risks and benefits associated with the use of the OTX-DP or PV are described below.

### 4.5.1. Potential Benefits

The benefits of OTX-DP are not yet known, but are thought to be:

- Reduction of signs and symptoms associated with allergic conjunctivitis.
- Improved treatment outcome through eliminating subject non-compliance with the use of daily drops.
- Improved treatment outcome through the delivery of therapeutic levels of dexamethasone continuously for the intended duration of therapy and the elimination of preservatives commonly found in ophthalmic preparations.

### 4.5.2. Potential Risks

In general, the following risks could occur from the insertion and use of the OTX-DP or PV:

- Ocular pain and discomfort
- Conjunctivitis
- Blepharitis
- Epiphora
- Ocular pruritus
- Perforation of or trauma to the punctum and/or surrounding tissues; or punctoplasty
- Allergic reaction
- Impaired visual acuity
- Chemosis
- Inflammatory reaction
- Canaliculitis
- Dacrocystitis

- Tearing with mucopurulent discharge
- Stenosis (narrowing/closing) of the punctum
- IOP elevation
- Cataract formation
- Increased risk of infection
- Infection that if severe could lead temporary or permanent impairment of sight
- Inability to remove the OTX-DP or PV

# 5. STUDY OBJECTIVES AND DESIGN

This is a prospective, multi-center, randomized, double-masked, vehicle-controlled study to evaluate the efficacy and safety of OTX-DP compared to PV for the treatment of the signs and symptoms of allergic conjunctivitis.

The modified Ora-CAC® model used in the current study has been developed to study the interactions between the early and late phases of the allergic response in the eye, and to evaluate the effects of pharmaceutical intervention. The modified CAC model utilizes 3 challenges conducted over a 2-day interval to evaluate the effectiveness of a test agent to: 1) prevent an acute ocular allergic reaction (the initial CAC), and 2) evaluate the test agent's ability to prevent an acute ocular allergic reaction in the presence of subclinical late phase inflammation (the latter re-challenge CACs).

The modified CAC model provides the opportunity to investigate the effects of the underlying inflammatory reaction on the ability of the tissues to mount a robust acute response to a subsequent allergen challenge. The modified CAC model also provides a means to investigate the mechanism(s) of action of anti-inflammatory agents in the treatment of allergic reactions.

This study will comprise of 13 office visits over a period of approximately 5 to 11 weeks. Visits 2, 3a, 3b, and 4a will be used to select a subject population that responds reproducibly to the 3 CACs administered over a 2-day interval used in the modified Ora-CAC model to induce the underlying inflammatory component characteristic of chronic allergic conjunctivitis. Subjects who meet the entry criteria for itching and redness response to the CAC at Visits 2, 3a, 3b, and 4a will be randomized at a 1:1 ratio (active:vehicle) at Visit 4b (Day 1) to receive one of the following treatment arms bilaterally:

- OTX-DP (N=40 subjects) or
- PV (N=40 subjects)

In the OTX-DP arm, subjects will receive bilateral OTX-DP (dexamethasone ophthalmic insert, 0.4mg) inserts.

The series of CACs and re-challenge CACs during Visits 5, 6a, and 6b will be used for the primary efficacy measures at Visit 6b and will assess the effectiveness of the OTX-DP (beginning at 5 days post-insertion, with the primary endpoint at 7 days post-insertion). Subjects will return to the office for Visits 7, 8a, and 8b for another series of CAC and re-challenge CACs and will return again for Visit 9 (Day 30+3) for the removal of OTX-DP or PV, if still present, and for final safety evaluations.

## 5.1. Study Objectives

To evaluate the efficacy and safety of OTX-DP as a dexamethasone ophthalmic insert when placed in the canaliculus of the eyelid for the treatment of the signs and symptoms of allergic conjunctivitis.

## 5.2. Clinical Hypothesis

Statistical hypotheses for the primary efficacy endpoint of ocular itching at Visit 6b are as follows:

$H_{10}$: There is no difference in mean ocular itching scores between OTX-DP and PV treated subjects for at least 1 of the 3 time points during Visit 6b.

$H_{1a}$: There is a difference in mean ocular itching scores between OTX-DP and PV treated subjects for all 3 time points during Visit 6b.

Similar hypotheses will be tested for the key secondary efficacy endpoints of ocular itching at Visits 5, 6a, 7, 8a, 8b. Statistical significance will be determined using a two-sided significance level of 0.05.

## 5.3. Efficacy and Safety Parameters

### 5.3.1. Primary Efficacy Evaluations

The primary endpoint is:

- Ocular itching evaluated by the subject on Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments)

### 5.3.2. Secondary Efficacy Evaluations

Key secondary outcomes are the measures of ocular itching at the following visits at 3(±1), 5(±1), and 7(±1) minutes post-CAC:

- Visit 6a (Day 8; 7 days post-insertion)
- Visit 5 (Day 7; 6 days post-insertion)
- Visit 8b (Day 15; 14 days post-insertion; 8 hours from Visit 8a)
- Visit 8a (Day 15; 14 days post-insertion)
- Visit 7 (Day 14; 13 days post-insertion)

Other secondary efficacy measures are ocular itching at Visits 5, 6a, 6b, 7, 8a, and 8b at the 10(±1) minutes post-CAC and the following assessments made at Visits 5, 6a, 6b, 7, 8a, and 8b at 7(±1), 15(±1), and 20(±3) minutes post-CAC:

- Conjunctival redness evaluated by the investigator (0-4 scale, allowing half unit increments)
- Ciliary and episcleral redness evaluated by the investigator (0-4 scale, allowing half unit increments)
- Chemosis evaluated by the investigator (0-4 scale, allowing half unit increments)
- Eyelid swelling evaluated by the subject (0-3 scale, NOT allowing half unit increments)
- Tearing/watery eyes evaluated by the subject (0-4 scale, NOT allowing half unit increments)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0-4 scale, NOT allowing half-unit increments)

- Nasal symptom composite score based on the assessments of rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion (analyzed as a qualitative measure determined as the presence or absence of at least one nasal symptom [present/absent], and as a quantitative measure calculated as the sum of the four component symptom scores [ranging from 0 to 16])

### 5.3.3. Safety Evaluations

- Adverse Events (AEs) (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) using an ETDRS chart
- Slit-lamp biomicroscopy, including punctum exam
- Intraocular Pressure (IOP)
- Dilated Fundoscopy Examination

## 5.4. Training of Investigators

Only ophthalmologists or optometrists who are experienced with punctal plug insertion will be considered for participation as Principal Investigators or Sub-Investigators in this study. All investigators who will use the OTX-DP or PV will undergo training on instructions for the insertion procedure which can be found in Appendix G.

## 5.5. Subject Selection

### 5.5.1. Study Population

Subjects of at least 18 years of age of either sex and of any race, who meet all of the inclusion criteria and none of the exclusion criteria.

### 5.5.2. Inclusion Criteria

*Each subject must:*

1. be at least 18 years of age of either sex and any race;
2. provide written informed consent and sign the HIPAA form;
3. be willing and able to follow all instructions and attend all study visits;
4. be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6 in Section 5.5.3).
5. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study period;
6. have a BCVA of greater than or equal to 50 ETDRS letters (20/100 Snellen equivalent or better) in each eye as measured at Visit 1;
7. agree to have urine pregnancy testing (for women considered capable of becoming pregnant, including 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]) performed at Visit 2 and at the exit visit; not be lactating; and agree to use a medically acceptable form of birth control throughout the clinical study duration;

8. have a positive history of ocular allergies and a positive skin test reaction to a perennial allergen (cat dander, dog dander, dust mites, cockroaches) and a seasonal allergen (trees, grasses, and/or ragweed) as confirmed by the allergic skin test conducted at Visit 1 or given to the subject within 24 months of the subject's Visit 2;
9. have a positive bilateral CAC reaction (defined as ≥ 2 itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;
10. have an average of ≥ 3 itching and ≥2.5 conjunctival redness for both eyes after the first three post-CAC assessment time points at Visit 4a.

### 5.5.3. Exclusion Criteria

*Each subject must not:*

1. have known contraindications or sensitivities to the use of any of the medications required by the protocol;
2. have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or study 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 a history of refractive surgery (including LASIK procedures) within the past 2 years;
4. have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5. have the presence of an active ocular infection (bacterial, viral or fungal), a current diagnosis or history of Herpes Simplex Keratitis, or a positive history of an ocular herpetic infection at any visit;
6. use any of the following disallowed medications* during the period indicated **prior to Visit 2** and during the study:

   **7 Days**

   - systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer drug combinations, H1 antihistamine- vasoconstrictor drug combinations;
   - decongestants;
   - monoamine oxidase inhibitors;
   - all other topical ophthalmic preparations (including artificial tears);
   - lid scrubs;
   - prostaglandins or prostaglandin derivatives;
   - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

   **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 2 and will continue to be maintained for the duration of the study.*

   **14 Days**

   - inhaled, ocular or topical corticosteroids or mast cell stabilizers;

   **45 Days**

   - depot-corticosteroids;

**2 Months**

- 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 study)

7. have a congenital or ocular anomaly (including punctal or lid ectropion, entropion, trichiasis, or supernumerary puncta) or anomalies of the punctum (including lack of good punctal apposition in both eyes);
8. have a diagnosis of any significant uncontrolled illness;
9. history of alcohol or drug abuse in the past year;
10. known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
11. have planned surgery (ocular or systemic) during the trial period or within 30 days after;
12. have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
13. be a female who is currently pregnant, planning a pregnancy, or lactating;
14. have a score of >0 for ocular itching and/or >1 for conjunctival redness prior to the challenge in either eye at Visit 2;
15. have an intraocular pressure that is less than 5 mmHg or greater than 22 mmHg or any type of glaucoma at Visit 2;
16. have had a history of an IOP increase as a result of steroid treatment;
17. have an unsuccessful transient punctum dilation to 0.7 mm prior to insertion of OTX-DP or PV;
18. be an employee of the site that is directly involved in the management, administration, or support of the study, or are an immediate family member of the same.

# 6. STUDY DATA COLLECTION

## 6.1. Study Schematic

The study Time and Event Schedule is presented in Appendix A.

## 6.2. Data Collection

Data collected from all study procedures and assessments will be collected and documented on the appropriate electronic Case Report Form (eCRF) for the study.

## 6.3. Subject Enrollment

All subjects screened for the study who sign a consent form will be assigned a 5-digit Screening number which will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in sequential order beginning with SXX001 where XX is a 2-digit site number.

Once a subject meets all qualification criteria, they will be randomly assigned to masked treatment using a 1:1 (OTX-DP: PV) assignment ratio. Subjects will be randomized on Visit 4b (Day 1) by assignment of the lowest 4-digit randomization number available at the investigative site, starting with RXX01, where XX is a 2-digit site number. No product numbers will be skipped or omitted. The investigational product will be inserted per the procedures outlined in Appendix G.

## 6.4. Masking

The Sponsor, Investigator and the subject will be masked to the treatment assignment throughout the subject's participation in the study. OTX-DP and PV are identical in appearance and will be supplied in identical packages so they cannot be distinguished by the user. If it is medically necessary to identify the product used, the Investigator will follow procedures outlined in Section 9.9.2.

## 6.5. Data Collection

Data collected from all study procedures and assessments will be collected and documented on the appropriate electronic Case Report Form (eCRF) for the study.

# 7. STUDY OBSERVATIONS AND PROCEDURES

## 7.1. Subject Screening and Informed Consent

Prior to a subject's participation in the study (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
Failure to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to remain in the clinic for all CAC titrations and procedures and be willing to return to the clinic for study Visits 2, 3a, 3b, 4a, 4b, 5, 6a, 6b, 7, 8a, 8b, and 9, as required.

Prior to the completion of the Screening Phase (Visit 1-4a), if it is determined a subject did not in fact meet eligibility criteria, the subject may be brought back at a later date to re-attempt the screening process.

Subjects can be re-screened a maximum of three times.

## 7.2. Screen Failures

A screen-fail will be defined as screened subjects who do not meet the inclusion/exclusion criteria prior to randomization at Visit 4b (Day 1).

## 7.3. Subject Withdrawal

Subjects may be discontinued prior to their completion of the study due to:

- adverse events
- protocol violations
- administrative reasons (eg, inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or study sponsor and will be clearly documented on the eCRF.

## 7.4. Product Quality Complaints

All product quality complaints of the OTX-DP or PV will be documented on the appropriate eCRF and reported to Ocular Therapeutix or designee within 24 hours. Ocular Therapeutix will advise whether the investigational product(s) is still suitable for use or, should be returned to the Sponsor for additional analysis and investigation. The product quality complaint will be included in the final analysis.

## 7.5. Treatment of OTX-DP or PV

Qualifying subjects will be randomized at Visit 4b (Day 1) to receive one of the following treatment arms bilaterally:

- OTX-DP (N=40 subjects) or
- PV (N=40 subjects)

In the OTX-DP arm, subjects will receive OTX-DP (dexamethasone, 0.4 mg) until insert absorption or removal (if needed), whichever comes first.

Randomization is at a 1:1 ratio (active:vehicle).

## 7.6. Concomitant Medications

A concomitant medication is any drug or substance administered from Visit 1 (Screening) through the last study visit, Visit 9 (Day 30). The generic name of the drug or substance, the dose, the route of administration, the duration of treatment (including the start and stop dates), the frequency, the indication, and whether or not the medication was taken due to an AE will be recorded for each drug or substance.

Subjects should be instructed not to start taking any new medications, including nonprescription drugs and herbal preparations, unless they have received permission from the Investigator. The use of any concurrent medication, prescription or over-the-counter (OTC), is to be recorded on the subject's

source document and corresponding eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational product study is not permitted.

## 7.7. Rescue Therapy

Cold compress should first be used in the management of allergic symptoms. Subjects may be prescribed anti-inflammatory or anti-allergy medication at the Investigator's discretion. If prescribed such anti-inflammatory or anti-allergy medication, the insert will not be removed and subjects will be followed for safety only.

Currently marketed over-the-counter anti-allergy eye drops (i.e., anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects at the end of the subject's last visit, after all evaluations are completed.

## 7.8. Early Loss of Insert and Patient Follow-up

If at any point post-insertion, the subject is experiencing discomfort or an undesirable reaction due to OTX-DP or PV, it may be removed per the instructions in Appendix H, and the subject should be exited (discontinued) at that time.

If only 1 insert is present at any visit prior to a subject's Exit Visit (Visit 9), that subject should continue in the study for safety. These subjects will not undergo the conjunctival allergen challenge and will therefore return for Visit 9. At this visit, the following procedures will be performed:

- Update of Medical/Medication History
- Assessment of Adverse Events
- Best Corrected Visual Acuity (BCVA) using an ETDRS chart
- Slit Lamp Examination, including punctum exam
- Visualization of OTX-DP or PV
- IOP Measurement
- Dilated Fundoscopy Examination

Intracanalicular inserts that are no longer present or removed at any point in the study will not be replaced.

# 8. STUDY ASSESSMENTS

At the screening visits (Visits 1, 2, 3a, 3b, and 4a), the subject's eligibility for study participation will be determined by checking all inclusion and exclusion criteria as specified in Section 5.5. If a subject fails one of the inclusion or exclusion criteria the subject will be a screening failure and no further assessments will be done.

Details of the procedures for these assessments can be found in the Appendices and both eyes should be evaluated at every visit.

## 8.1. Visit 1 - Screening (Day -45 to -6)

- *Informed Consent/HIPAA:* Prior to any changes in a subject's medical treatment and/or study visit procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA authorization form.

- *Demographic data:* Demographic data will be recorded.
- *Allergic Skin Test (if applicable)*: A diagnostic test for allergic disease (skin test) will be performed according to Ora, Inc. SOPs if there is no documented skin test within the past 24 months. Subjects may receive either anti-itch cream or calamine lotion (depending on the washout) after the skin test has been completed.
- *Medical/medication/ocular and non-ocular history:* Collect and record all medical history, any medications and any underlying condition(s). Current underlying conditions, including those that began within the last sixty days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within the sixty days prior to Visit 2.
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart:* Subjects must have a BCVA of greater than or equal to 50 ETDRS letters (20/100 Snellen equivalent or better). See Appendix C.
- *Review of Inclusion/Exclusion Criteria:* Confirm with subjects if washout from any current medications and instruct them to follow the appropriate washout time periods (refer to Section 5.5)

## 8.2. Visit 2 (Day -5+1 day) CAC screening / titration

- *Update of Medical/Medication History*
- *Urine Pregnancy Test (for females of childbearing potential):* Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled. See Appendix B.
  - Note: If a female has a positive pregnancy test during the study, then the investigator will notify the pharmacovigilance team immediately (See Section 9.5). The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to the pharmacovigilance team and Sponsor as required.
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart.* See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess initial ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix I, Appendix J and Appendix K). Subjects exhibiting signs and/or symptoms of allergic conjunctivitis (defined as >1 redness in conjunctival bed or the presence of any itching in either eye) will be excluded.
- *Slit Lamp Biomicroscopy:* A slit-lamp exam, including punctum exam, will be performed in both eyes to exclude subjects with disallowed ocular conditions (see Appendix D). Findings of abnormality which are not exclusionary should be recorded as Medical History.
- *Review of Inclusion/Exclusion Criteria*
- *Titration Conjunctival Allergen Challenge:* A conjunctival allergen challenge (CAC) will be performed bilaterally with a perennial or seasonal allergen (serially diluted in buffered

saline and administered via a micropipette). One drop of a solubilized allergen to which the subject is sensitized, at the weakest dilution, will be instilled bilaterally into the conjunctival cul-de-sac.

- If the subject fails to react within 10 (±2) minutes, increasingly concentrated doses may be instilled bilaterally at approximately ten-minute intervals until a positive reaction is elicited. If increasing doses are required (i.e., for insufficient bilateral itching as assessed by the subject and/or redness as evaluated by the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen, other allergens to which the subject is sensitized may be used starting at the lowest dose.
- A positive CAC at Visit 2 is defined as a score of > 2 for redness in the conjunctival vessel bed of each eye and > 2 for itching in both eyes within 10 (±2) minutes of receiving that dose of allergen. Any subject who fails to test positively will be excluded from the study.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Upon completion of the CAC, subjects will receive ocular examination by the investigator to evaluate all investigator evaluated efficacy variables and confirm the subject's qualification. Subjects will be asked to assess their ocular and nasal symptoms.
- *IOP Measurement:* For subjects eliciting a positive post-CAC reaction, intraocular pressure (IOP) will be measured in each eye by contact tonometry. This assessment will be considered baseline. See Appendix E.
- *Dilated Fundoscopy Examination:* For subjects eliciting a positive post-CAC reaction, a dilated fundoscopy examination will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology. All findings should be recorded as Medical History. This assessment will be considered baseline. See Appendix F.

## 8.3. Visit 3a (Day -4+1 day) CAC confirmation #1)

- *Update of Medical/Medication History*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix I, Appendix J and Appendix K).
- *Slit Lamp Biomicroscopy:* A slit lamp exam, including punctum exam, will be performed to exclude subjects with disallowed ocular conditions (see Appendix D). Findings of abnormality which are not exclusionary should be recorded as Medical History.
- *Review of Inclusion/Exclusion Criteria*
- *Confirmation Conjunctival Allergen Challenge:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 2, will be administered bilaterally.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*: Assessment of itching will be made by the subject at 3(±1), 5(±1), and 7(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1) and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.4. Visit 3b (Day -4+1 day; 8 hours post V3a) CAC confirmation #2

- *Update of Medical/Medication History*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart.* See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam:* A slit-lamp exam, including punctum exam, will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality which are not exclusionary should be recorded as Medical History. See Appendix D.
- *Review of Inclusion/Exclusion Criteria*
- *Confirmation Conjunctival Allergen Challenge:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 2, will be administered bilaterally. Challenge will occur 8 hours +1 hour following the Visit 3a challenge.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), and 7(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1) and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.5. Visit 4a (Day -3+1 day; 24±6 hours post V3a) CAC confirmation #3

- *Update of Medical/Medication History*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam:* A slit-lamp exam, including punctum exam, will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality which are not exclusionary should be recorded as Medical History. See Appendix D.
- *Review Inclusion and Exclusion Criteria*
- *Baseline Conjunctival Allergen Challenge:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 2, will be administered bilaterally. Challenge will occur 24±6 hours following the Visit 3a challenge.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).
- If the subject fails to react positively (i.e., an average of ≥ 3 itching and ≥2.5 conjunctival redness) in both eyes after the first three post-CAC assessment time points, he/she will be excluded from the study.
- *Review Inclusion and Exclusion Criteria*

## 8.6. Visit 4b (Day 1): Randomization/Insertion of OTX-DP or PV

- *Update of Medical/Medication History*
- *Enrollment and Randomization:* Subjects who meet entry criteria and qualify to continue in the study will be enrolled and randomly assigned to undergo the insertion of either OTX-DP or PV. Subjects will be assigned the lowest 4-digit randomization number available, starting with RXX01, where XX is a 2-digit site number. No randomization numbers will be skipped or omitted.
- *Insertion of OTX-DP or PV:* The Investigator will either insert OTX-DP or PV bilaterally based on the randomization schedule and according to the procedures outlined in Appendix G. The time of insertion will be recorded.
- *Visualization of OTX-DP or PV*: The Investigator will visualize correct placement of the intracanalicular inserts according to the procedures outlined in Appendix G.
- *Adverse Event Query:* Adverse Events will be monitored after the initial attempt of insertion of OTX-DP or PV. All adverse events will be promptly reviewed by the investigator for accuracy and completeness. All adverse events will be documented on the appropriate eCRF.

## 8.7. Visit 5 (Day 7; 6 days post-insertion) CAC #1

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart.* See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of OTX-DP or PV*
- *Conjunctival Allergen Challenge:* Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.8. Visit 6a (Day 8; 7 days post-insertion) CAC re-challenge #2

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.

- *Visualization of Intracanalicular Inserts.* See Appendix G.
- Conjunctival Allergen Challenge: Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.9. Visit 6b (Day 8; 8 hours from Visit 6a) CAC re-challenge #3

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of Intracanalicular Inserts*. See Appendix G.
- *Conjunctival Allergen Challenge:* Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2. Challenge will occur 8 hours +1 hour following the Visit 6a challenge.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).
- *IOP Measurement.* See Appendix E.

## 8.10. Visit 7 (Day 14; 13 days post-insertion) CAC re-challenge #1

- Update of Medical/Medication History
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of OTX-DP or PV.* See Appendix G.
- *Conjunctival Allergen Challenge:* Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the

investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.11. Visit 8a (Day 15; 14 days post-insertion) CAC re-challenge #2

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of Intracanalicular Inserts*. See Appendix G.
- *Conjunctival Allergen Challenge:* Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).

## 8.12. Visit 8b (Day 15; 8 hours from Visit 8a) CAC re-challenge #3

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of Intracanalicular Inserts*. See Appendix G.
- *Conjunctival Allergen Challenge:* Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2. Challenge will occur 8 hours +1 hour following the Visit 8a challenge.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), 7(±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±3) minutes post- challenge (see Appendix I, Appendix J and Appendix K).
- *IOP Measurement*. See Appendix E.

## 8.13. Visit 9 (Day 30+3): Study Exit

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Urine Pregnancy Test:* This will be given to all women of childbearing potential. See Appendix B.
- *Best Corrected Visual Acuity (BCVA) using an ETDRS chart*. See Appendix C.
- *Slit Lamp Biomicroscopy including punctum exam*. See Appendix D.
- *Visualization of Intracanalicular Inserts*. See Appendix G.
- *IOP Measurement*. See Appendix E.
- *Dilated Fundoscopy*. See Appendix F.
- *Intracanalicular Inserts Removal:* If the intracanalicular inserts are still present at this visit, ***and*** the subject is experiencing any symptoms related to the inserts, the Investigator will remove the insert(s) according to the procedures outlined in Appendix H. Asymptomatic subjects may leave the office at the completion of visit assessments without removal of inserts.
- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.
- *Study Exit*

## 8.14. Early Discontinued Subjects

Subjects may voluntarily withdraw from the study at any time. Subjects who withdraw consent or are withdrawn per investigator discretion will be considered early discontinued subjects and should complete the exit visit assessments required at Visit 9.

## 8.15. Unscheduled Visits

For unscheduled visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

These visits may be performed in order to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit pages of the source document and corresponding eCRF for randomized subjects.

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit), include:

- Assessment of Adverse Events
- Assessment of Concomitant Medications
- Best Corrected Visual Acuity (BCVA) using an ETDRS chart
- Urine Pregnancy Test (for females of childbearing potential)
- Slit lamp Biomicroscopy including punctum examination

- Visualization of Intracanalicular Inserts
- IOP Measurement
- Dilated Fundoscopy

If a randomized subject does not attend their scheduled visit, eCRF pages for missed visits will be skipped. All efforts should be made to schedule the subject for an Exit Visit (Visit 9) to complete exit procedures.

Inserts that are no longer present or removed at any point in the study will not be replaced.

# 9. ADVERSE EVENTS

The investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the Investigator will question the subject about adverse events using an open question taking care not to influence the subject's answers, e.g. "have you noticed any change in your health?"

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

## 9.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction
- Signs, symptoms of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- A laboratory abnormality occurring after the administration of the IP that results in subject withdrawal from the study or medical treatment or further follow-up.

Any medical events experienced pre-treatment, resulting from protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen) should be captured as medical history.

## 9.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalizations for elective surgeries do not constitute an SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life- threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.

## 9.3. Disease-Related Events or Outcomes Not Qualifying as AE/SAEs

Not applicable

## 9.4. Monitoring and Recording of AEs and SAEs

### 9.4.1. Adverse Events

Any AE experienced by the subject from Visit 4b (Randomization/Insertion) through Visit 9 (30 day follow-up visit) is to be recorded in the eCRF, regardless of the severity of the event or its relationship to study treatment.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

### 9.4.2. Serious Adverse Events

Any SAE experienced by the subject from Visit 4b (Randomization/Insertion) through Visit 9 (30 day follow-up visit) is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

### 9.4.3. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 9.2.
- The severity of the event as defined in Section 9.7.1.
- The relationship of the event to study treatment as defined in Section 9.7.2.

## 9.5. Immediate Reporting of Serious Adverse Events and Pregnancies

In order to adhere to all applicable laws and regulations for reporting an SAE or pregnancy, the study site must formally notify the pharmacovigilance team within 24 hours of the study site staff becoming aware of the SAE or pregnancy. It is the Investigator's responsibility to ensure that the SAE or pregnancy reporting information is emailed or faxed as described in Figure 2. It may be necessary for the pharmacovigilance team to directly communicate with the Investigator if additional information is required.

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the pharmacovigilance team on the subject's condition within 24 hours. New or updated information will be recorded on the SAE reporting form. The updated SAE reporting form should be sent to the pharmacovigilance team within 24 hours as described in Figure 2.

All additional follow-up evaluations must be reported to the pharmacovigilance team. Such data should be sent by fax or email (Figure 2) within 10 calendar days. All SAEs will be followed until the Investigator and Ocular Therapeutix agree that the event is satisfactorily resolved.

## 9.6. Death

The death must be recorded on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the pharmacovigilance team.

**Figure 2 Reporting Information for SAEs and Pregnancies**

To report initial or follow up SAE or Pregnancy information email or fax a copy of the SAE or Pregnancy report form to the following:
ProPharma Group
**Email: clinicalsafety@propharmagroup.com**
**Fax: +1-866-681-1063**

## 9.7. Evaluating AEs and SAEs

### 9.7.1. Severity

The following definitions should be considered when evaluating the severity of AEs and SAEs:

- *Mild* Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities
- *Moderate* Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities
- *Severe* Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities

For AEs that change in intensity, the start and stop date of each intensity should be recorded.

An AE that is assessed as severe should not be confused with a SAE. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.2 "Definition of a SAE."

### 9.7.2. Relationship to OTX-DP or PV or procedure

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

| | |
|---|---|
| UNRELATED | This category applies to those (S)AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.); there is no reasonable probability that the (S)AE may have been caused by the insertion procedure or the intracanalicular insert. If the investigator determines that the AE is unlikely to be related to the study drug, then this would be the appropriate category. |
| RELATED | The following criteria should be applied in considering inclusion of an (S)AE in this category:<br>1. It bears a reasonable temporal relationship to the insertion procedure or the presence of the intracanalicular insert<br>2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other factors (e.g., disease under study, concurrent disease(s) and concomitant medications) and modes of therapy administered to the subject<br>3. It disappears or decreases on removal of the intracanalicular insert<br>4. It follows a known pattern of response to the insertion procedure or the intracanalicular insert |

### 9.7.3. Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure (IB); as determined by Ocular Therapeutix, Inc.

## 9.8. Pre-scheduled or Elective Procedures or Routinely Scheduled Treatments

A pre-scheduled or elective procedure or routinely scheduled treatment will not be allowed during the study period.

## 9.9. Procedures for Handling Special Situations

### 9.9.1. Pregnancy

Females should not become pregnant during the study period. If this occurs the subject should notify the Investigator immediately. The Investigator must report the pregnancy as outlined in Section 9.5. In addition, the Investigator or study site staff must report the outcome of the pregnancy to the pharmacovigilance team.

### 9.9.2. Unmasking for Medical Emergencies

In the case of a medical emergency or occurrence of an SAE, the randomization code may be un-masked and made available to the Investigator, Sponsor, and/or other study personnel involved in the conduct of the study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject, as medically required. If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency, the Investigator may call the Medical Monitor and notify the Sponsor. The treatment assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, this leaving the masking of the remaining subjects intact.

The site will receive one emergency unmasking envelope for every product received and the envelopes should be stored in a secured location. The envelopes and product will both be labeled with the same randomization number. The envelopes are sealed and contain the unmasked treatment information for the corresponding study product.

Ocular Therapeutix will make the final determination if the unmasking request will be granted. Once the unmasking request is granted the investigator or designee should identify and retrieve the emergency unmasking envelope for the given subject. The emergency unmasking envelope should be opened by the designated site personnel. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

Subjects will have the investigational product removed immediately if treatment assignment is unmasked.

#### 9.9.3. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Ocular Therapeutix to be associated to the study treatment administered. Ocular Therapeutix will report SUSARs to the appropriate authorities within the required regulatory timeframes. Reports of SUSARs will be made to IRBs, and Investigators, as needed.

# 10. STATISTICAL ANALYSIS

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), and qualitative/categorical data will be summarized using frequencies and percentages.

## 10.1. Study Populations

### 10.1.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all subjects who are randomized. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

### 10.1.2. Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) with no major protocol violations that would impact the efficacy of the drug. This population will be analyzed as treated using observed data only for confirmatory analyses.

### 10.1.3. Safety Population

The Safety population includes all randomized subjects who received the IP. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

## 10.2. Primary Efficacy Variables

The primary efficacy variable is:

- Ocular itching evaluated by the subject on Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments)

## 10.3. Secondary Efficacy Variables

Key secondary outcomes are the measures of ocular itching at 3(±1), 5(±1), and 7(±1) minutes post-CAC at the following visits:

- Visit 6a (Day 8; 7 days post-insertion)
- Visit 5 (Day 7; 6 days post-insertion)
- Visit 8b (Day 15; 14 days post-insertion; 8 hours from Visit 8a)
- Visit 8a (Day 15; 14 days post-insertion)
- Visit 7 (Day 14; 13 days post-insertion)

Other secondary efficacy measures are ocular itching at Visits 5, 6a, 6b, 7, 8a, and 8b at the 10(±1) minutes post-CAC and the following assessments made at Visits 5, 6a, 6b, 7, 8a, and 8b at 7(±1), 15(±1), and 20(±3) minutes post-CAC:

- Conjunctival redness evaluated by the investigator (0-4 scale, allowing half unit increments)
- Ciliary and episcleral redness evaluated by the investigator (0-4 scale, allowing half unit increments)
- Chemosis evaluated by the investigator (0-4 scale, allowing half unit increments)
- Eyelid swelling evaluated by the subject (0-3 scale, NOT allowing half unit increments)
- Tearing/watery eyes evaluated by the subject (0-4 scale, NOT allowing half unit increments)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0-4 scale, NOT allowing half-unit increments)
- Nasal symptom composite score based on the assessments of rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion (analyzed as a qualitative measure determined as the presence or absence of at least one nasal symptom [present/absent], and as a quantitative measure calculated as the sum of the four component symptom scores [ranging from 0 to 16])

## 10.4. Statistical Hypotheses

Statistical hypotheses for the primary efficacy endpoint of ocular itching at Visit 6b are as follows:

$H_{10}$: There is no difference in mean ocular itching scores between OTX-DP and PV treated subjects for at least 1 of the 3 time points during Visit 6b.

$H_{1a}$: There is a difference in mean ocular itching scores between OTX-DP and PV treated subjects for all 3 time points during Visit 6b.

Similar hypotheses will be tested for the key secondary efficacy endpoints of ocular itching at Visits 5, 6a, 7, 8a, 8b. Statistical significance will be determined using a two-sided significance level of 0.05.

## 10.5. Adjustment for Multiplicity

All six sets of hypotheses described in the previous section will be tested in a hierarchical order, testing the primary hypotheses first (corresponding to Visit 6b), and then proceeding with the key secondary efficacy hypotheses in the order presented below.

1. Visit 6b
2. Visit 6a
3. Visit 5
4. Visit 8b
5. Visit 8a
6. Visit 7

If at any point in the hierarchical order statistical significance is not demonstrated, testing will stop, and the remaining tests will be deemed not statistically significant.

There will be no adjustment necessary for testing multiple time points within a visit, as statistical significance at all three post-CAC® time points are required for a visit to be deemed statistically significant.

## 10.6. Sample Size

Approximately 80 subjects will be randomized at Visit 4b in a 1:1 ratio across the two treatment arms (40 OTX-DP; 40 PV). Up to approximately 10 additional subjects may be enrolled to make up for any subjects who did not complete Visit 6b CAC procedures.

A total of 40 subjects in each treatment arm will provide 97.0%, 99.8%, and 99.9% power to demonstrate a statistically significant difference in ocular itching between OTX-DP and PV treated subjects at each of the 3, 5, and 7 minute post-CAC time points of Visit 6b, respectively, assuming a treatment difference of 0.87 units at 3 minutes post-CAC, 1.08 units at 5 minutes post-CAC, and 1.13 units at 7 minutes post-CAC; a standard deviation of 1.0 unit at all time points; and a two-sided Type I error of 0.05.

Assuming independence between time points, 40 subjects per group will have at least 96.7% power to demonstrate a statistically significant difference over all three primary post-CAC time points at Visit 6b for ocular itching between OTX-DP and PV treated subjects.

## 10.7. General Imputation Methods

Missing data for the primary efficacy variable will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation techniques on the ITT population, producing twenty “complete” (imputed) datasets which will then be analyzed separately. Results from the separate analyses on the twenty “complete” datasets will be combined for presentation through the use of SAS PROC

MIANALYZE. A separate imputation model will be fit for each time point. The model will include variables for treatment, baseline measure, and response measure.

For sensitivity analysis, the ITT population will also be analyzed using the following:

- Observed data only
- Last observation carried forward (LOCF)
- Worst case observation (WCO)
- Baseline observation carried forward (BOCF)

For the LOCF imputation, only post-challenge observations within the same visit will be carried forward. Therefore, there must be post-challenge values available at post-baseline visits to implement LOCF, as pre-challenge values will not be carried forward to post-challenge values and the prior visit values will not be carried forward to the following visit values. Missing values post-challenge will be carried forward from the last observed time point within the same visit, i.e., a missing 5-minute observation at Visit 5b will be imputed from the 3-minute observation from Visit 5b, etc.

For the WCO imputation, missing data due to a subject being prescribed anti-inflammatory or anti-allergy medication will be imputed using the worst possible outcome (maximum observed value) from the subject's treatment group, starting at the first time point at which a subject takes an anti-inflammatory or anti-allergy medication.

For the BOCF imputation, missing data post-baseline will be imputed with the corresponding time point baseline data from Visit 4a.

## 10.8. Primary Efficacy Analyses

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), 7(±1) minutes post- CAC® (0-4 scale, allowing half unit increments) at Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a). The average of each subject's eyes at each post-CAC® time point will be used as the unit of analysis for ocular itching. Ocular itching will be analyzed using an ANCOVA model for each post-CAC® time point at Visit 6b, with the time appropriate post- CAC® scores at Visit 4a as a covariate and treatment group as the sole factor (OTX-DP compared to PV). Two-sample t-tests will be used as unadjusted sensitivity analyses at each post-CAC® time point, as well as a non-parametric Wilcoxon rank sum tests (OTX-DP compared to PV). At each post-CAC® time point, a two-sided significance level of $\alpha = 0.05$ will be used to determine statistical significance of treatment differences.

The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population using the multiple imputation MCMC method for missing data as described previously. Sensitivity or supportive analyses will be performed on the ITT population using observed data only and the LOCF, BOCF and WCO methods. The PP population will also be analyzed using observed data only as a sensitivity analysis.

## 10.9. Secondary Efficacy Analyses

Analyses will be performed on quantitative secondary endpoints in a manner similar to the primary endpoint. Qualitative measures will be analyzed using a Fisher's exact test or Chi- Square test as appropriate (OTX-DP compared to PV). Secondary endpoints include ocular itching (except at Visit 6b at 3(±1), 5(±1), and 7(±1) minutes post-CAC), conjunctival redness, episcleral and ciliary redness, chemosis, eyelid swelling, tearing/watery eyes, rhinorrhea, nasal pruritus, ear or palate pruritus, nasal congestion, and a composite score (analyzed as a qualitative measure determined as the presence or absence of at least one nasal symptom [present/absent], and as a quantitative measure calculated as

the sum of the four component symptom scores [ranging from 0 to 16]). The secondary endpoints will be analyzed for the ITT population with observed data only and for the PP population with observed data only.

In addition, quantitative analyses will include ANCOVA models which will be run at each visit, with treatment, time point, and time appropriate baseline as covariates for adjustment (accounting for repeated measurements). Least Square Means (LS Means) for each treatment, the corresponding 95% confidence intervals (CIs), and the estimated treatment difference between OTX-DP and PV will be calculated from these ANCOVA models.

## 10.10. Demographics and Baseline Data

The demographic and baseline medical history data will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

## 10.11. Safety Analyses

Incidence of adverse events will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Slit lamp biomicroscopy, dilated fundoscopy examination, visual acuity, and IOP will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

# 11. GENERAL INFORMATION

## 11.1. Study Termination

Ocular Therapeutix reserves the right to discontinue the study at any stage, with suitable written notice to the Investigator and the IRB/IEC and other regulatory authorities as appropriate. Similarly, the Investigator may withdraw from participation in the study after providing written notification to Ocular Therapeutix within 30 days of their intent to withdraw. However, Ocular Therapeutix and the Investigator will be bound by their obligation to complete the follow-up of subjects already treated in the clinical study. The subjects must be followed according to the clinical protocol and information obtained during subject follow-up shall be reported on eCRFs.

All Serious AEs will be evaluated and if the Sponsor determines that unreasonable risk to the subject is possible, the study will be terminated, and all regulatory authorities and the participating Investigator(s) will be notified. Termination shall occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first provides notice of the effect.

A terminated study may not be resumed without the local IRB/IEC or regulatory authority approval, as required.

## 11.2. Monitoring

The Investigator and the investigating center will permit authorized clinical research personnel and clinical study monitors assigned by Ocular Therapeutix to source verify completed eCRFs, and review IRB/IEC decisions, and Investigator and clinical site records at regular intervals throughout the study. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations and/or institution policies prohibit the direct examination of records by the study Sponsor or

designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Further details of the study monitoring procedures will be outlined in a Monitoring Plan.

If the monitor discovers that the Investigator is not complying with the signed Investigator Agreement, the protocol, or other applicable regulations, or any conditions of approval imposed by the reviewing IRB/IEC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, investigational product shipments to the Investigator may be discontinued and the Investigator's participation in the clinical study may be terminated. The monitor shall also require such an Investigator to dispose of or return the unused product, unless this action would jeopardize the rights, safety or welfare of a subject.

## 11.3. Retention of Documentation

The Investigator will maintain all study related documentation including all correspondence, records of financial interest, individual subject records, informed consent forms, all drug product accountability records, the protocol with any/all amendments, all correspondence with and approval from the IRB/IEC, the clinical study agreement, and copies of eCRFs data for 2 years after the latter of the following dates:

1. The date a marketing application is approved for the drug for the indication for which it is being studied, or
20. The date that the records are no longer required for purposes of supporting an application to a regulatory agency.

The files may be discarded only upon notification from Ocular Therapeutix. To avoid error, the Investigator should contact Ocular Therapeutix before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

## 11.4. Other Study Supplies

Clarity HCG (RAC Medical Boca Raton, FL) will be used for pregnancy tests. Ora, Inc. will supply these pregnancy kits.

The allergens used for the skin test and conjunctival allergen challenge (cat dander, dog dander, dust mites, cockroach, grasses, ragweed, and trees) will be supplied by and reconstituted by Ora, Inc.

Relief drops will be supplied by Ora, Inc.

## 11.5. Photos and Videos

The Investigator may be asked to record before, during, and/or after IP insertion, visualization, and/or removal procedures and to collect photographs of the eye. The videos and photographs should be identified only using the subject number and subject initials and should not contain any identifiers such as the subject's name or birth date. The video and photographs will be used for training, advertising or in scientific conferences, journals or magazines.

# 12. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS AND ADMINISTRATIVE ISSUES

The study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and consistent with the 1996 version of the Declaration of Helsinki.

## 12.1. Protection of Human Subjects

The protection of human subjects will follow the regulations of the United States and will be the responsibility of the Principal Investigator.

## 12.2. Compliance with Informed Consent Regulations

An IRB/IEC approved consent form, signed and dated by both the subject and the delegated study staff presenting the consent, is required from each subject prior to enrollment into the study, and before any study specific procedures are initiated.

If at any point during the subject's participation in the study the Informed Consent Form requires revision (e.g., due to a protocol amendment or significant new safety information) it is the Investigator's responsibility to ensure that the revised ICF is reviewed by Ocular Therapeutix and approved by the IRB/IEC. The updated IRB/IEC approved Informed Consent Form must be presented to the subject, and signed and dated by both the subject, and the study staff presenting the consent as per IRB/IEC requirements.

## 12.3. Compliance with IRB/IEC Regulations

The Investigator must obtain approval from the appropriate IRB/IEC prior to initiating the study and continuing review approval per IRB/IEC policy.

## 12.4. Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure the confidentiality of the data in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ocular Therapeutix, the IRB/IEC approving this study, and other regulatory agencies, as appropriate, will be granted direct access to the study subjects' original medical and study records for verification of the data and/or clinical trial procedures.

# 13. STORAGE AND ACCOUNTABILITY OF OTX-DP AND PV

## 13.1. Product Storage

OTX-DP and PV inserts must be stored in a secure area accessible only to the Investigator and his/her designee(s) and must be stored refrigerated between 2ºC and 8ºC. Brief excursions up to 25±2°C are permitted; temperature excursions should be reported to Ocular Therapeutix to determine product suitability for use.

## 13.2. Product Accountability

The intracanalicular insert is to be administered only by qualified Investigators in accordance with the protocol, and only to subjects enrolled in the study.

## 13.3. Product Return and Disposal

After product accountability has been verified by the monitor, unused intracanalicular inserts can be destroyed by following the site's established written destruction procedures. If the site does not have written destruction procedures the unused product will be returned to Ocular Therapeutix at the completion of the study or upon request by the Sponsor. The return details will be documented on the accountability form.

# 14. APPENDICES

# APPENDIX A. TIME AND EVENT SCHEDULE

| **Visit**<br>**Visit Window** | V1<br>-45 to -6 | V2<br>-5+1 | V3a<br>-4+1 | V3b[1]<br>(V3a+8hrs) | V4a[2]<br>(V3a+24±6 hrs) | V4b<br>(2-3 days post V3a) | V5<br>7 | V6a<br>8 | V6b[1]<br>(V6a+8hrs) | V7<br>14 | V8a<br>15 | V8b[1]<br>(V8a+8hrs) | V9<br>30+3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Day** ***(Number of days post insertion)*** | | | | | | | 6 | 7 | 7 | 13 | 14 | 14 | 29-32 |
| **PROCEDURE** | | | | | | | | | | | | | |
| **General Assessments** | | | | | | | | | | | | | |
| Informed Consent & HIPAA | X | | | | | | | | | | | | |
| Demographic Data | X | | | | | | | | | | | | |
| Medical & Medication History | X | | | | | | | | | | | | |
| Update Medical & Medication History | | X | X | X | X | X | X | X | X | X | X | X | X |
| Allergic Skin Test | X | | | | | | | | | | | | |
| Urine Pregnancy Test[3] | | X | | | | | | | | | | | X |
| Randomization | | | | | | X | | | | | | | |
| AE Assessment | | | | | | X | X | X | X | X | X | X | X |
| **Allergen Challenge** | | | | | | | | | | | | | |
| CAC | | X[4] | X[5] | X[5] | X[5] | | X | X[6] | X[6] | X[6] | X[6] | X[6] | |
| Signs and Symptoms Assessments[7] | | X | X | X | X | | X | X | X | X | X | X | |
| **Visual/Systems Exams** | | | | | | | | | | | | | |
| Best Corrected Visual Acuity | X | X | X | X | X | | X | X | X | X | X | X | X |
| Slit Lamp Biomicroscopy including punctum exam | | X | X | X | X | | X | X | X | X | X | X | X |

| **Visit**<br><br>**Visit Window** | V1<br><br>-45 to -6 | V2<br><br>-5+1 | V3a<br><br>-4+1 | V3b[1]<br><br>(V3a+8hrs) | V4a[2]<br><br>(V3a+24±6 hrs) | V4b<br><br>(2-3 days post V3a) | V5<br><br>7 | V6a<br><br>8 | V6b[1]<br><br>(V6a+8hrs) | V7<br><br>14 | V8a<br><br>15 | V8b[1]<br><br>(V8a+8hrs) | V9<br><br>30+3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Day**<br>***(Number of days post insertion)*** | | | | | | | 6 | 7 | 7 | 13 | 14 | 14 | 29-32 |
| Intracanalicular Insert Visualization | | | | | | X | X | X | X | X | X | X | X |
| IOP [8] | | X | | | | | | | X | | | X | X |
| Dilated Fundoscopy Examination | | X | | | | | | | | | | | X |
| **Study Therapy** | | | | | | | | | | | | | |
| Digital Photographs/Videos[9] | | | | | | X | X | X | X | X | X | X | X |
| IP Insertion | | | | | | X | | | | | | | |
| Removal of Inserts | | | | | | | | | | | | | X[10] |
| Exit from Study | | | | | | | | | | | | | X |

[1] Visits 3b, 6b, and 8b to occur 8 hours + 1 hour after Visits 3a, 6a, and 8a respectively.
[2] Visit 4a to occur 24±6 hours after Visit 3a.
[3] At Visits 2 and 9, for all women of childbearing potential.
[4] Titration CAC
[5] Confirmatory CAC
[6] Re-challenge CAC
[7] Ocular (itching; conjunctival, episcleral, and ciliary redness; chemosis; eyelid swelling; tearing/watery eyes) and Nasal (pruritis; rhinorrhea; ear or palate pruritis; congestion) pre- and post- CAC
[8] Measured following the last CAC assessments when all other evaluations are complete
[9] Digital photographs and/or videos may be taken of each subject's eyes before, during, and/or after IP insertion, visualization, and/or removal.
[10] If the inserts are still present, and the subject is experiencing symptoms related to the inserts, the Investigator will remove them according to the removal procedures. Inserts do not need to be removed for asymptomatic subjects.

# APPENDIX B. PREGNANCY TESTING

Female subjects of childbearing potential will have a urine pregnancy test read at the site at Visit 2 and Visit 9 (or Exit Visit). Pregnancy tests (Clarity HCG urine test strips, RAC Medical Boca Raton, FL) will be used.

# APPENDIX C. VISUAL ACUITY PROCEDURES (ETDRS CHART)

Visual acuity should be evaluated at the beginning of each study visit. Every effort should be made to have the same BCVA assessor throughout the study period. Visual acuity testing should be done starting with most recent correction.

BCVA should be measured using a backlit ETDRS chart such as Precision Vision's or equivalent. It is recommended that the site use a backlit, wall-mounted or caster stand ETDRS distance eye chart with a luminance of 85cd/$m^2$ set at 4 meters from the subject. A trial lens frame, or phoropter, set at 12.0 mm vertex distance should be used to obtain manifest refraction measurements. If possible, final refinement of sphere should be done at 4 meters with a trial lens set.

EYE CHARTS

All distance visual acuity measurement should be made using an Illuminator Box (or equivalent) set at 4 meters from the subject. Any subject unable to read at least 20 or more letters on the ETDRS chart at 4 meters should be tested at 1 meter according to the instructions provided for 1 meter testing. The fluorescent tubes in the light box should be checked periodically for proper functioning.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary, and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR VISUAL ACUITY CALCULATIONS

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N × 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR visual acuity for that eye.

For example: subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

| | |
|---|---|
| Base logMAR | = 0.1 |
| N (total number of letters incorrect on line 0.2 as well as 0.1) | = 4 |
| N x T (T=0.02) | = 0.08 |
| Base logMAR + (N x T) | = 0.1 + 0.08 |
| **logMAR VA** | **= 0.18** |

BCVA examination should begin with the right eye (OD). The procedure should be repeated for the left eye (OS).

The subject must sit for the 1-meter test. The avoidance of any head movement forward or backward is particularly important during this test.

| Letter Score | LogMAR Value | Snellen Equivalent |
|---|---|---|
| 5 | 1.6 | 20/800 |
| 10 | 1.5 | 20/640 |
| 15 | 1.4 | 20/500 |
| 20 | 1.3 | 20/400 |
| 25 | 1.2 | 20/320 |
| 30 | 1.1 | 20/250 |
| 35 | 1.0 | 20/200 |
| 40 | 0.9 | 20/160 |
| 45 | 0.8 | 20/125 |
| 50 | 0.7 | 20/100 |
| 55 | 0.6 | 20/80 |
| 60 | 0.5 | 20/63 |
| 65 | 0.4 | 20/50 |
| 70 | 0.3 | 20/40 |
| 75 | 0.2 | 20/32 |
| 80 | 0.1 | 20/25 |
| 85 | 0.0 | 20/20 |
| 90 | −0.1 | 20/15 |
| 95 | −0.2 | 20/12 |

LogMAR = logarithm of the minimal angle of resolution.

# APPENDIX D. SLIT LAMP BIOMICROSCOPY PROCEDURES

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). For any finding of "abnormal clinically significant", the Investigator will provide any relevant explanation/comment on the case report form. The following will be examined:

- Eyelids including all four punctum and surrounding area
- Conjunctiva
- Sclera
- Cornea
- Anterior chamber
- Iris
- Lens

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

# APPENDIX E. PROCEDURE FOR EVALUATING IOP

Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. A single measurement is made to obtain a determination of IOP. Reasonable efforts should be made to use the same tonometer employing the investigator's standard technique throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

# APPENDIX F. DILATED FUNDOSCOPY

Dilated fundoscopy exams will be performed using direct and indirect ophthalmoscopy. The investigator will make observations of the vitreous, retina, macula, choroid and optic nerve. Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the investigator that may interfere with trial parameters or otherwise confound the data) and those that are not clinically significant will be described. An indirect fundoscopy examination should be performed if retinal disease is detected. It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects. The use of cyclopentolate 1% ophthalmic solution is recommended as secondary dilating medication, should the need arise.

# APPENDIX G. INSERTION AND VISUALIZATION INSTRUCTIONS

For qualifying subjects, the Investigator will conduct an insertion of either the OTX-DP or PV as per the randomization list at Visit 4b (Day 1). The area of the punctum should be anesthetized with either a topical anesthetic instilled into the conjunctival sac or an anesthetic soaked, cotton- tipped Weck-Cel™ spear or equivalent held against the punctum for 30 seconds.

The size of the punctum will be assessed utilizing a standard punctum size gauge. If the punctum is less than 0.7 mm wide, it should be dilated using a standard punctum dilator tool.

***To insert the OTX-DP or PV:***

Using forceps, grasp the OTX-DP or PV and insert it into the punctum as per the instructions in the Prescribing Information:

Do not use if pouch has been damaged or opened. Do not re-sterilize.

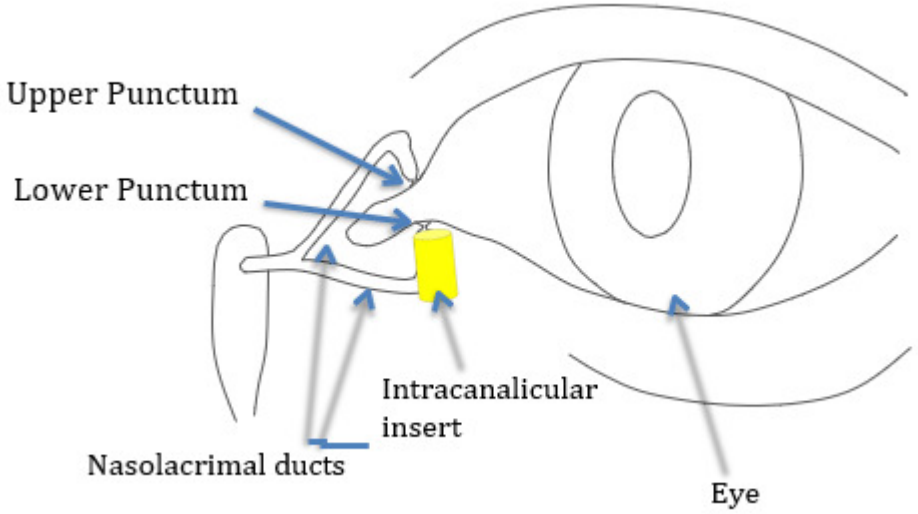
21. Carefully remove foam carrier and transfer to a clean and dry area.
22. If necessary, dilate the punctum with an ophthalmic dilator. Care should be taken not to perforate the canaliculus during dilation or insertion of OTX-DP or PV. If perforation occurs, do not insert OTX-DP or PV.
23. After drying the punctal area, using blunt (non-toothed) forceps, grasp OTX-DP or PV and insert into the lower lacrimal canaliculus. OTX-DP or PV should be placed just below the punctal opening. Excessive squeezing of OTX-DP or PV may cause deformation.
24. To aid in the hydration of OTX-DP or PV, 1 to 2 drops of balanced salt solution can be instilled into the punctum. OTX-DP or PV hydrates quickly upon contact with moisture. If OTX-DP or PV begins to hydrate before fully inserted, discard the product and use a new OTX-DP or PV.

OTX-DP or PV can be visualized when illuminated by a blue light source (e.g., slit lamp or hand held blue light) with yellow filter.

*Note: If protrusion or partial extrusion occurs, the intracanalicular insert may be repositioned.*

The intracanalicular inserts should rest within the canaliculus just beyond the punctal opening as shown Figure 3 After insertion and exposure with tear film, the inserts will rapidly hydrate and expand to fill the vertical portion of the canalicular cavity.

**Figure 3 Placement of OTX-DP or PV in the Canaliculus**




**OTX-DP or PV Presence by Visual Technique**

The Investigator will assess the presence of the insert at Visits 4b, 5, 6a, 6b, 7, 8a, 8b, and 9 by using a slit lamp with a blue light and yellow filter.

# APPENDIX H. INSERT REMOVAL INSTRUCTIONS

The intracanalicular inserts can be removed either via application of manual pressure or saline irrigation, as described below.

**Application of Manual Pressure**

1. Apply topical anesthesia
2. Identify the insert visually through the punctum tissue.
3. Dilate the punctum and canaliculus (if necessary)
4. Place the blunt end of an instrument, e.g. punctum dilator or equivalent, next to the distal end of the insert.
5. Apply gentle pressure by pressing on the instrument in an outward motion towards the punctum, until the insert is expressed out of the punctum**.**

**Saline Irrigation**

1. Ensure the punctum and canaliculus is sufficiently dilated.
2. Fill a sterile syringe and fixed cannula with sterile saline.
3. Insert the cannula into the vertical canaliculus.
4. Insert until it stops, and simultaneously rotate the syringe horizontally.
5. Press slowly on the syringe plunger to flush the insert.
6. In order to help assess whether the flush is complete, it may be helpful to ask the subject to report when they taste saline or feel it in their nose.

# APPENDIX I. APPENDIX I. ALLERGEN CHALLENGE SCALES- OCULAR SYMPTOMS

Subject-Evaluated Ocular Symptoms

Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale

**Itching:**

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

**0.5 unit increments ARE allowed**

Ora Calibra™ Conjunctival Allergen Challenge Eyelid Swelling Scale

**Eyelid Swelling:**

**0 = None**
**1.0 = Mild** – Detectable swelling of lower and/or upper lid
**2.0 = Moderate** – Definite swelling of lower and/or upper lid
**3.0 = Severe** – Swelling of lower and/or upper lid to the point that there is a decrease in the space between your upper and lower lids

**0.5 unit increments ARE NOT allowed**

Ora Calibra™ Conjunctival Allergen Challenge Tearing/Watery Eyes Scale

**Tearing/Watery Eyes:**

**0 = None/Normal**
**1 = Mild** – A noticeably increased moistening of your eye
**2 = Moderate** – Your eye feels "full" of water; your lashes feel a little wet
**3 = Severe** – Feels like tears might drip down your face; very wet lashes
**4 = Very Severe** – Tears are dripping down your face

**0.5 increments ARE NOT allowed**

**Ora proprietary scales – Not for distribution without permission**

# APPENDIX J. ALLERGEN CHALLENGE SCALES- NASAL SYMPTOMS

Subject-Evaluated Nasal Symptoms Ora Calibra™ Rhinorrhea Scale

**Rhinorrhea (Runny Nose):**

**0= None**
**1= Mild** (sensation of nasal mucus flowing down nasal passage; no discharge present)
**2= Moderate** (may be associated with post nasal drip; nasal mucus flow more pronounced; will need to blow nose soon)
**3= Moderate/Severe** (nasal mucus discharge requiring occasional wiping with Kleenex)
**4= Severe** (uncontrolled nasal discharge; requiring frequent wiping and blowing nose)

**0.5 unit increments ARE NOT allowed.**

Ora Calibra™ Nasal Pruritus Scale

**Nasal Pruritus (Itchy Nose):**

**0= None**
**1= Mild** (An intermittent tickle sensation)
**2= Moderate** (A mild continuous itch)
**3= Moderate/Severe** (A severe itch with desire to rub)
**4= Severe** (Incapacitating itch with an irresistible urge to rub)

**0.5 unit increments ARE NOT allowed.**

Ora Calibra™ Ear or Palate Pruritus Scale

**Ear or Palate Pruritus (Itchy Ear or Palate):**

**0= None**
**1= Mild** (An intermittent tickle sensation)
**2= Moderate** (A mild continuous itch)
**3= Moderate/Severe** (A severe itch with desire to rub)
**4= Severe** (Incapacitating itch with an irresistible urge to rub)

**0.5 unit increments ARE NOT allowed.**

Ora Calibra™ Nasal Congestion Scale

**Nasal Congestion:**

**0= None** (No breathing difficulty)
**1= Mild** (Some sensation of blockage)
**2= Moderate** (Partial Blockage)
**3= Moderate/Severe** (Significant blockage but can still breathe through nose)
**4= Severe** (Cannot breathe through nose at all)

**0.5 unit increments ARE NOT allowed.**

**Ora proprietary scales – Not for distribution without permission**

# APPENDIX K. INVESTIGATOR-EVALUATED SIGNS (OCULAR)

Ora Calibra™ Ocular Hyperemia Scale

**Regional Redness: Hyperemia (ciliary, conjunctival, and episcleral). All evaluated separately by an Investigator with the slit lamp**

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

**0.5 unit increments ARE allowed**

**Ora CalibraTM Chemosis Scale**

**Chemosis:**

**0 =** None
**1.0 =** Detectable only by slit lamp beam; definite separation of conjunctiva from sclera
**2.0** = Visible in normal room light; more diffuse edema
**3.0 =** Conjunctival billowing at the limbus; very diffuse and noticeable
**4.0 =** Severe overall billowing of conjunctiva

**0.5 unit increments ARE allowed**

**Ora Proprietary Scales – Not for distribution without permission**

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