# Clinical Trial Protocol: 913/22-100-0006

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| **Protocol Title:** | A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Pharmacokinetics of Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution, Used Two Times Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis) |
| **Protocol Number:** | 913/22-100-0006 |
| **Study Phase:** | 3 |
| **Investigational Product Name:** | Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution |
| **IND Number:** | 153035 |
| **Indication:** | Allergic Conjunctivitis |
| **Investigators:** | Multi-Center |
| **Sponsor:** | Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Contract Research Organization:** | Ora, Inc.<br>300 Brickstone Square, Third Floor<br>Andover, MA 01810 |
| **IRB/IEC:** | Alpha IRB<br>1001 Avenida Pico, Suite C, #497<br>San Clemente, CA 92673 |
| **Original Protocol:** | Date: 13 Feb 2023 |
| **Amendment 1:** | Date: 07 Jul 2023 |

## Confidentiality Statement

## SPONSOR PERSONNEL

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| **Sponsor:** | Bausch & Lomb Incorporated<br>400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Sponsor Representative:** | [redacted] |

## ORA PERSONNEL

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|---|---|
| **Department Vice President:** | [redacted] |
| **Project Manager:** | [redacted] |

## MEDICAL MONITOR

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|---|---|
| **Medical Monitor:** | [redacted] |

## SYNOPSIS

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| **Protocol Title:** | A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Pharmacokinetics of Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution, Used Two Times Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis) |
| **Protocol Number:** | 913/22-100-0006 |
| **Investigational Product:** | Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution |
| **Study Phase:** | 3 |
| **Primary Objective(s):** | To compare the safety and tolerability of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution versus its vehicle in healthy adult subjects and in pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis). |
| **Secondary Objective(s):** | To characterize the plasma pharmacokinetics (PK) of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution following a single dose and 22-day BID topical ocular dosing in a subset of healthy adult subjects. |
| **Overall Study Design:** | |
| **Structure:** | The study will consist of 4-5[1] study visits: a Screening Visit may be conducted to verify subjects are eligible to participate and, following randomization at Day 1, a Treatment Period of 6 weeks to evaluate the safety of brimonidine tartrate/ ketotifen fumarate combination drug product compared to its vehicle.<br>Screening Period: At the Screening or Visit 1 (Day 1) (if Screening and Visit 1 are done on the same day), subjects will sign the informed consent form (ICF) and have their medical/medication history collected. |

[1] Screening Visit and Visit 1 may be conducted on the same day.

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| | Treatment Period: Treatment will begin at Visit 1 after subjects are randomized 2:1 to receive either brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution or vehicle ophthalmic solution bilaterally. At this visit, subjects will instill/receive an in-office dose of the treatment they were randomized to receive. A subset of 25 healthy adult subjects will undergo PK blood drawspre- (IP) instillation and out to 4 hours post- IP instillation. Qualified subjects will be dispensed the assigned IP and a diary for at-home dosing. Visits 2 and 3 are safety follow-up visits, and subjects will receive one dose in the office. For the PK subset, blood draws will also be performed at Visit 3 following the in-office dose. Subjects will instill/receive a final dose of study medication at-home the evening prior to Visit 4. |
| **Duration:** | This trial consists of 4-5 office visits over a period of approximately 6-10 weeks. |
| **Controls:** | Vehicle of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% ophthalmic solution |
| **Dosage Instillation:** | At Visit 1, a trained study technician will observe the subject, subject's caregiver, or subject's parent/legal guardian (if applicable for subjects less than 18 years of age) instill 1 drop of the assigned IP into each eye. The subjects enrolled to the PK subset will receive 1 drop of the assigned IP into each eye from a trained technician. At-home dosing will begin following Visit 1.<br>At Visit 2 and 3, a trained study technician will instill 1 drop of the assigned IP into each eye in-office.<br>At home, subjects, subject's caregiver or subject's parent/legal guardian (if applicable, for subjects less than 18 years of age), will instill at-home dosing in each eye BID 7.5 hours apart for up to 6 consecutive weeks (until the evening prior to Visit 4). |
| **Summary of Visit Schedule:** | **Screening Period (Day -28 to Day 1)[1]:** Screening<br>**Treatment Period:**<br>**Visit 1 (Day 1, Baseline):** Baseline Assessments, Enrollment/Randomization, and In-office Instillation<br>**Visit 2 (Day 8 ± 2):** Follow-up<br>**Visit 3 (Day 22 ± 3):** Follow-up<br>**Visit 4 (Day 43 + 3):** Treatment Discontinuation & Exit Visit |

[1] Screening Visit and Visit 1 may be conducted on the same day

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| **Measures Taken to Reduce Bias:** | Randomization will be used to avoid bias in the assignment of subjects to IP, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Finally, masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints. |
| **Study Population Characteristics:** | |
| **Number of Subjects:** | Approximately 600 subjects will be screened in order to enroll approximately 501 subjects from approximately 6 sites in the United States. Of the subject total, approximately 100 pediatric subjects are anticipated to be enrolled into this study.<br>The age classification for the pediatric population will be approximately 50 subjects in each of the following groups:<br>• 5-12 years old<br>• 13-17 years old<br>Subjects will not be stratified by age group when assigned to IP.<br>A subset of up to 25 healthy adult subjects (~16 subjects for the IP and ~9 subjects for the vehicle) will undergo PK blood draws to assess the systemic exposure of brimonidine and ketotifen. |
| **Condition/Disease:** | Allergic Conjunctivitis |
| **Inclusion Criteria:** | Subjects must:<br>1. be at least 5 years of age at Screening Visit or Visit 1 (if Screening and Visit 1 are done on the same day), of either sex and any race (a government issued ID and/or birth certificate will be verified at the time ICF is signed);<br>2. provide written informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. Subjects who are at least 7 years of age and less than 18 years of age will need to sign an assent form. In addition, all subjects below the age of 18 years will be required to have both parents or legal guardian sign the informed consent;<br>3. be willing and able to follow all instructions and attend all study visits (and be accompanied by a parent/legal guardian if the subject is under the age of 18); |

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| | 4. be able to self-administer eye drops satisfactorily or have a caregiver or parent/legal guardian (if applicable, for subjects less than 18 years of age) at home[1] routinely available for this purpose;<br>5. for subjects less than 18 years of age, have either a history or family history of atopic disease (such as atopic dermatitis, asthma, allergic conjunctivitis/rhinitis, and atopic keratoconjunctivitis (AKC));<br>6. (if female and of childbearing potential) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and at exit visit[2]; must not be lactating; and must agree to use at least 1 medically acceptable form of birth control throughout the study duration and for at least 14 days prior to Visit 1 and 1 month after discontinuing IP. Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject), spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of male partner at least 3 months prior to the first dose of investigational drug (Visit 1). Note: Women considered capable of becoming pregnant include 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);<br>7. (if male and with female partner of childbearing potential) must use at least 1 medically acceptable form of birth control. Note: Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to receiving IP (Visit 1). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository throughout the study duration, for at least 14 days prior to and 1 month after discontinuing IP;<br>8. have ocular health within normal limits, including a calculated (VA) of 0.3 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, |

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| | Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score;<br>9. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a body mass index (BMI) ≥18 and ≤34 lbs/in$^2$ and a minimum body weight of 99 lbs;<br>10. (for selected healthy adult subjects agreeing to undergo PK blood draws) have suitable venous access for blood sampling. |
| **Exclusion Criteria:** | Subjects may <u>not</u>:<br>1. have known contraindications or sensitivities to the use of any of the IP medication or components;<br>2. have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;<br>3. have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;<br>4. have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;<br>5. use any of the following disallowed medications during the period indicated prior to Visit 1 and during the study;<br><u>5 days</u><br>• artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular corticosteroids, ocular antihistamines, and any other topical ophthalmic agents;<br><u>14 days</u><br>• any systemic medications which the investigator feels may confound study data or interfere with subject's study participation;<br>6. have used contact lenses within 24 hours prior to each visit (Visit 1, 2, 3, and 4);<br>7. have prior (within 7 days of beginning IP) or currently active significant illness that could compromise participation, in the opinion of the investigator; |

[1] If a caregiver or parent/legal guardian will administer eye drops, then he/she must be present at Visit 1 to administer eye drops in-office.
[2] For identified premenarchal females at Visit 1, their menarchal status will be queried at each subsequent visit. If a subject is no longer premenarchal at any of her subsequent visits, that subject must agree to have a urine pregnancy test performed at that visit. Subsequently these subjects will follow all the requirements of female subjects of childbearing potential regarding pregnancy tests and birth control.

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| | 8. have prior (within 30 days of beginning IP) or anticipated concurrent use of an IP or device during the study period;<br>9. have been randomized in study 909 or 910 conducted by Bausch & Lomb;<br>10. be an employee or family member of employee at the investigative site;<br>11. have an ocular or systemic condition or is in a situation that the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's study participation;<br>12. have planned surgery (ocular or systemic) during the trial period or within 30 days after;<br>13. have body weight below the 5$^{th}$ percentile for their age (subjects 12 years of age or younger only) (see Appendix 2);<br>14. be a female who is currently pregnant, is planning a pregnancy, or lactating;<br>15. have an abnormal blood pressure (defined as $\leq 90$ or $\geq 160$ (systolic) measured in mmHg or $\leq 60$ or $\geq 100$ (diastolic) measured in mmHg). For pediatric subjects, abnormal blood pressure is defined as $\geq 140$ (systolic) measured in mmHg or $\geq 90$ (diastolic) measured in mmHg;<br>16. have an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg or have a normal IOP with a prior diagnosis/history of glaucoma at Visit 1;<br>17. have symptoms associated with COVID-19 or have been in contact with someone diagnosed with COVID-19 within 14 days of the Screening Visit or Visit 1 (if Screening and Visit 1 are done on the same day);<br>18. (for selected healthy adult subjects agreeing to undergo PK blood draws) have excessive consumption of caffeine- or xanthine-containing beverages (more than 4 cups or servings per day) within 48 hours prior to dosing at Visit 1 or for the duration of the study (see Appendix 6);<br>19. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a history of tobacco, nicotine, or nicotine-containing product use within 12 months prior to Visit 1;<br>20. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a history or current evidence of drug or alcohol abuse within 12 months prior to Visit 1; |

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| | 21. (for selected healthy adult subjects agreeing to undergo PK blood draws) have blood donation or equivalent blood loss of >450 mL within 60 days prior to Visit 1. |
| **Study Formulations and Formulation Numbers:** | **Test Article:** Brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution, containing [redacted]<br>**Vehicle Control:** Vehicle ophthalmic solution, containing BAK, glycerin, mannitol, povidone, and water for injection. Hydrochloric acid and/or sodium hydroxide may be used to adjust pH. |
| **Safety Measures:** | • Adverse Events (AE) (reported, elicited, and observed)<br>• Urine Pregnancy Test<br>• Visual Acuity using an ETDRS chart<br>• Slit Lamp Biomicroscopy<br>• Intraocular Pressure (should be performed on subjects ≥ 10 years old)<br>• Physical Examination<br>• Vital Signs (resting blood pressure and pulse)<br>• Dilated Fundus Examination |
| **Tolerability Measures:** | Drop comfort assessment [redacted] assessed by subjects ≥ 10 years of age immediately upon instillation, at 30 seconds, and at 1-minute post-instillation at Visits 1, 2, and 3 |
| **Pharmacokinetic Measures:** | Blood samples will be collected from the PK population at pre-dose, 0.25 (±3 min), 0.5 (±5 min), 1 (±10 min), 2 (±10 min), and 4 (±20 min) hours following the first topical ocular instillation of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution or vehicle on Day 1 and also on Day 22 to measure the plasma concentrations of brimonidine and ketotifen. If the data allows, the following PK parameters will be estimated: $C_{max}$, $C_{min}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-4h}$, and accumulation ratio ($R_{Cmax}$ and $R_{AUC}$). |
| **General Statistical Methods and Types of Analyses**<br>Statistical analyses will be detailed in the Statistical Analysis Plan.<br>Safety<br>All safety data will be analyzed using the safety population. Safety of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution compared to its vehicle will be assessed by the review of all safety parameters. The examination conducted prior to | |

the first IP dose instillation at Visit 1 is defined as the baseline examination. The pre-instillation examination for Visit 2 and Visit 3 is defined as pre-instillation examination at those visits.

Changes (from the Visit 1 pre-instillation Baseline observation to all observations at later study visits and from pre-instillation to 15 minutes (+3 minutes) post IP instillation at each Visits 1-3) in biomicroscopy findings will be presented at each visit by treatment group. Similarly, changes from Baseline at Visit 4 in intraocular pressure and dilated fundoscopy findings will be presented by treatment group. In addition, changes at each visit (from the Visit 1 Baseline value) in VA will be presented by treatment group. IOP and Visual acuity changes from baseline will also be presented using categorical summaries.

A summary of physical examination results and a summary of vital signs will be presented at each applicable visit by treatment group.

Drop comfort will be summarized using descriptive statistics.

The quantitative variables will be summarized using descriptive statistics (e.g., number of observations (n), mean, standard deviation (SD), minimum, median, and maximum). The qualitative variables will be summarized using counts and percentages.

The number of subjects reporting any treatment emergent adverse event (TEAE) during the study will be presented. The number of subjects for each AE category (ocular and non-ocular) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, preferred term within each system organ class, for each treatment group. The number of subjects reporting serious AEs (SAEs) and AEs related to IP will also be tabulated. In addition, AEs will also be summarized by severity. Treatment emergent ocular AEs will also be summarized at the eye level for all treated eyes.

Subgroup analyses will be performed by age groups: 5-12 years old, 13-17 years old, 18-64 years old, and for ages greater than 64 years. Subgroup analyses will be performed on the following endpoints: AEs, IOP, VA, biomicroscopy, dilated fundoscopy, and tolerability.

Pharmacokinetics

Statistical analysis plasma concentrations will be based on the PK population, which will include all subjects with at least one blood sample drawn post-dose in the subset of subjects for PK blood draws. Pharmacokinetic parameter analyses will be performed using standard non-compartmental analysis, data permitting. When possible, plasma concentrations by scheduled time point and PK parameters by day will be summarized using descriptive statistics: n, mean, median, SD, minimum, maximum, and percent coefficient of variation (% CV).

**Summary of Known and Potential Risks and Benefits to Human Subjects**

Refer to Investigator's Brochure (IB).

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AC | allergic conjunctivitis |
| AKC | atopic keratoconjunctivitis |
| AE | adverse event |
| BAK | benzalkonium chloride |
| BCVA | best-corrected visual acuity |
| BID | twice daily |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| CFR | Code of Federal Regulations |
| CV | coefficient of variation |
| DHHS | Department of Health and Human Services |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ERC | ethical review committee |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GPC | giant papillary conjunctivitis |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IOP | Intraocular pressure |
| IP | investigational product |
| IRB | institutional review board |
| ISAAC | International Study of Asthma and Allergies in Childhood |
| logMAR | logarithm of the minimum angle of resolution |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | not clinically significant |
| NHANESIII | Third National Health and Nutrition Examination Survey |
| OD | right eye |
| OS | left eye |
| PAC | perennial allergic conjunctivitis |
| PHI | protected health information |
| PK | pharmacokinetics |
| RTSM | Randomization and Trial Supply Management |
| SAC | seasonal allergic conjunctivitis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |

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| SD | standard deviation |
| TEAE | treatment emergent adverse event |
| VA | visual acuity |
| VKC | vernal keratoconjunctivitis |

# 1 INTRODUCTION

Allergy is described as the fifth leading group of chronic diseases, affecting 50 million Americans. The Third National Health and Nutrition Examination Survey (NHANESIII) recently revealed that 40% of this American test population reported having episodes of ocular allergy (Singh, 2010). In a recent review of studies on the incidence of allergic conjunctivitis (AC) (Rosario, 2011), a previous study (Bielory, 2000) was updated that provided data on children and adolescents who participated in the International Study of Asthma and Allergies in Childhood (ISAAC) from as many as 57 countries. This ongoing effort revealed an increased prevalence from 16.5% in 1985 to 29.6% in 2000 (Steering Committee, 1998; Bjorksten, 2008). Other reports ranged from 41.4% for persons having at least one episode in 12 months, to 20.7% for those having 4 or more episodes (Hesselmar, 2001).

Ocular allergy ranges in severity from mild forms, which still interfere significantly with quality of life, to severe cases characterized by potential impairment of visual function. The term ocular allergy refers to a collection of hypersensitivity disorders that affect the lid, conjunctiva and/or cornea. Various clinical forms are included in the classification of ocular allergy: seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC) and contact or drug-induced dermo-conjunctivitis.

SAC and PAC are the most common allergic diseases, accounting for almost 90% of ocular allergic manifestations. Seasonal flux is usual when one or multiple pollen sensitizations are involved, however, in a mild climate AC might not disappear completely in the colder seasons, and is perennial when caused by sensitization to ubiquitous antigens such as mites and animal dander. These common ocular allergic diseases can be the most difficult of the allergic eye diseases to diagnose because no typical or exclusive signs and symptoms can be defined. The chronic forms, VKC, AKC and GPC, are relatively rare but clinically well characterized. Each of these diseases has specific clinical features in terms of diagnosis, pharmacological and non-pharmacological management (Abelson, July 2003).

Current therapies used for the treatment of AC include antihistamines, mast cell stabilizers, and dual-action therapies. While many of these therapies are effective in providing temporary relief, there remains an unmet need specifically for patients affected by more chronic forms of ocular allergy.

The purpose of this study is to evaluate the safety of Brimonidine Tartrate 0.025%/ Ketotifen Fumarate 0.035% combination ophthalmic solution compared to its vehicle in a population of healthy adult subjects and in pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis). Alaway® (ketotifen fumarate, 0.035%) is a second generation histamine H1 antagonist and is currently approved for the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander (Abelson, May 2003; Alaway® Ketotifen Fumarate Ophthalmic Solution, 0.035% Label approved April 2021). Lumify® (brimonidine tartrate, 0.025%) is a selective alpha2-AR agonist that acts as a topical vasoconstrictor for relief of ocular redness.

When used as directed, Lumify® did not demonstrate tachyphylaxis and virtually no rebound redness was observed (Ackerman, 2019; Lumify® Brimonidine Tartrate Ophthalmic Solution, 0.025% . Label approved September 2020). By combining the antihistamine ketotifen fumarate with the vasoconstrictor brimonidine tartrate, the combination is intended to utilize the unique attributes of each active agent to reduce ocular itching and redness for up 8 hours, while maintaining a safe profile. In addition, pharmacokinetics (PK) data will be collected in a subset of healthy adult subjects in the study to assess the systemic exposure of brimonidine and ketotifen following a single dose and 22-day BID topical ocular dosing.

## 2 STUDY OBJECTIVES

The primary objective is to compare the safety and tolerability of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution versus its vehicle in healthy adult subjects and in pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis).

The secondary objective is to characterize the plasma PK of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution following a single dose and 22-day BID topical ocular dosing in a subset of healthy adult subjects.

## 3 CLINICAL HYPOTHESES

It is hypothesized that the combination product will be safe and tolerable compared to the vehicle in a population of healthy adult subjects and pediatric subjects with a history or family history of atopic disease (including allergic conjunctivitis).

## 4 OVERALL STUDY DESIGN

This is a multi-center, double-masked, randomized, vehicle-controlled, parallel-group, safety study. Approximately 600 subjects will be screened in order to enroll approximately 501 subjects from approximately 6 sites. Of the subject total, approximately 100 pediatric subjects are anticipated to be enrolled into this study.

The age classification for the pediatric population will be approximately 50 subjects in each of the following groups:

- 5-12 years old
- 13-17 years old

Subjects will not be stratified by age group when assigned to IP.

A subset of up to 25 healthy adult subjects (~16 subjects for the IP and ~9 subjects for the vehicle) will undergo PK blood draws to assess the systemic exposure of brimonidine and ketotifen.

Subjects, subject's caregiver, or subject's parent/legal guardian (if applicable, for subjects less than 18 years of age), will instill 1 drop of the assigned investigational drug in each eye BID 7.5 hours apart for up to 6 consecutive weeks.

Subjects will have visits on Day 8 (±2), Day 22 (±3), and Day 43 (+3) for safety evaluations.

# 5 STUDY POPULATION

## 5.1 Number of Subjects (approximate)

Approximately 600 subjects will be screened in order to enroll approximately 501 subjects.

## 5.2 Study Population Characteristics

Healthy adult subjects (≥18 years of age) who do not have any conditions, in the investigator's opinion, that may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

**AND**

Pediatric subjects (5-17 years of age) with a history or family history of atopic disease (including allergic conjunctivitis).

## 5.3 Inclusion Criteria

Subjects must:

1. be at least 5 years of age at Screening Visit or Visit 1 (if Screening and Visit 1 are done on the same day), of either sex and any race (a government issued ID and/or birth certificate will be verified at the time ICF is signed);
2. provide written informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. Subjects who are at least 7 years of age and less than 18 years of age will need to sign an assent form. In addition, all subjects below the age of 18 years will be required to have both parents or legal guardian sign the informed consent;
3. be willing and able to follow all instructions and attend all study visits (and be accompanied by a parent/legal guardian if the subject is under the age of 18);
4. be able to self-administer eye drops satisfactorily or have a caregiver or parent/legal guardian (if applicable, for subjects less than 18 years of age) at home[1] routinely available for this purpose.
5. for subjects less than 18 years of age, have either a history or family history of atopic disease (such as, asthma, atopic keratoconjunctivitis, allergic conjunctivitis/rhinitis, and atopic dermatitis (AKC));
6. (if female and of childbearing potential) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and at exit visit[2]; must not be lactating;

[1] If a caregiver or parent/legal guardian will administer eye drops, then he/she must be present at Visit 1 to administer eye drops in-office.
[2] For identified premenarchal females at Visit 1, their menarchal status will be queried at each subsequent visit. If a subject is no longer premenarchal at any of her subsequent visits, that subject must agree to have a urine pregnancy test performed at that visit. Subsequently these subjects will follow all the requirements of female subjects of childbearing potential regarding pregnancy tests and birth control.

and must agree to use at least 1 medically acceptable form of birth control throughout the study duration and for at least 14 days prior to and 1 month after discontinuing IP. Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject), spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of male partner at least 3 months prior to the first dose of investigational drug (Visit 1). Note: Women considered capable of becoming pregnant include 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);

7. (if male and with female partner of childbearing potential) must use at least 1 medically acceptable form of birth control. Note: Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to receiving IP (Visit 1). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository throughout the study duration, for at least 14 days prior to and 1 month after discontinuing IP;
8. have ocular health within normal limits, including a calculated visual acuity (VA) of 0.3 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score;
9. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a body mass index (BMI) $\geq$18 and $\leq$34 lbs/in$^2$ and a minimum body weight of 99 lbs;
10. (for selected healthy adult subjects agreeing to undergo PK blood draws) have suitable venous access for blood sampling.

## 5.4 Exclusion Criteria

Subjects may <u>not</u>:

1. have known contraindications or sensitivities to the use of any of the IP medication or components;
2. have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
3. have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
4. have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;

5. use any of the following disallowed medications during the period indicated prior to Visit 1 and during the study:

   5 days

   - artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular corticosteroids, ocular antihistamines, and any other topical ophthalmic agents;

   14 days

   - any systemic medications which the investigator feels may confound study data or interfere with subject's study participation.

6. Have used contact lenses within 24 hours prior to each visit (Visit 1, 2, 3, and 4);
7. have prior (within 7 days of beginning IP) or currently active significant illness that could compromise participation, in the opinion of the investigator;
8. have prior (within 30 days of beginning IP) or anticipated concurrent use of an IP or device during the study period;
9. have been randomized in study 909 or 910 conducted by Bausch & Lomb;
10. be an employee or family member of employee at the investigative site;
11. have an ocular or systemic condition or is in a situation that the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's study participation;
12. have planned surgery (ocular or systemic) during the trial period or within 30 days after;
13. have body weight below the 5$^{th}$ percentile for their age (subjects 12 years of age or younger only) (see Appendix 4);
14. be a female who is currently pregnant, is planning a pregnancy, or lactating;
15. have an abnormal blood pressure (defined as $\leq 90$ or $\geq 160$ (systolic) measured in mmHg or $\leq 60$ or $\geq 100$ (diastolic) measured in mmHg). For pediatric subjects, abnormal blood pressure is defined as $\geq 140$ (systolic) measured in mmHg or $\geq 90$ (diastolic) measured in mmHg;
16. have an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg or have a normal IOP with a prior diagnosis/history of glaucoma at Visit 1;
17. have symptoms associated with COVID-19 or have been in contact with someone diagnosed with COVID-19 within 14 days of the Screening Visit or Visit 1 (if Screening and Visit 1 are done on the same day);
18. (for selected healthy adult subjects agreeing to undergo PK blood draws) have excessive consumption of caffeine- or xanthine-containing beverages (more than 4 cups or servings per day) within 48 hours prior to dosing at Visit 1 or for the duration of the study (see Appendix 6)

19. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a history of tobacco, nicotine, or nicotine-containing product use within 12 months prior to Visit 1;
20. (for selected healthy adult subjects agreeing to undergo PK blood draws) have a history or current evidence of drug or alcohol abuse within 12 months prior to Visit 1;
21. (for selected healthy adult subjects agreeing to undergo PK blood draws) have blood donation or equivalent blood loss of >450 mL within 60 days prior to Visit 1.

### 5.5 Withdrawal Criteria (if applicable)

Subjects may voluntarily withdraw from the study at any time.

Additionally, subjects may be discontinued for safety reasons as determined by the investigator (see Section 8.6.2).

## 6 STUDY PARAMETERS

### 6.1 Safety Measures

- AEs; reported, elicited and observed
- Urine Pregnancy Test
- Best-Corrected Visual Acuity (BCVA) using an ETDRS chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure (should be performed on subjects ≥ 10 years old)
- Physical Examination
- Vital Signs (resting blood pressure and pulse)
- Dilated Fundus Examination

### 6.2 Tolerability Measures

Drop comfort assessment (0-10 scale) assessed by subjects ≥ 10 years of age immediately upon instillation, at 30 seconds, and at 1 minute post-instillation at Visits 1, 2, and 3.

### 6.3 Pharmacokinetic Measures

Blood samples will be collected from the PK population at pre-dose, 0.25 (±3 min), 0.5 (±5 min), 1 (±10 min), 2 (±10 min), and 4 (±20 min) hours following the first topical ocular instillation of brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution or vehicle on Day 1 and also on Day 22 to measure the plasma concentrations of brimonidine and ketotifen. Details on collection, preparation, and shipping of blood samples are provided in the Laboratory Manual. All samples from both active and placebo groups will be analyzed. Upon request for data inspection, the bioanalytical lab may be unblinded. If the data allows, the following PK parameters will be estimated: $C_{max}$, $C_{min}$, $T_{max}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}4h}$, and accumulation ratio ($R_{Cmax}$ and $R_{AUC}$).

| Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum observed plasma concentration |
| $C_{min}$ | Minimum observed plasma concentration |
| $T_{max}$ | Time of maximum observed plasma concentration |
| $AUC_{0-t}$ | Area under the plasma drug concentration-time curve from time 0 to the last quantifiable drug concentration |
| $AUC_{0-4h}$ | Area under the plasma drug concentration-time curve from time 0 through 4 h |
| $R_{Cmax}$ | Accumulation ratio of $C_{max}$ at steady-state to $C_{max}$ after the first dose |
| $R_{AUC}$ | Accumulation ratio of $AUC_{0-t}$ at steady-state to $AUC_{0-t}$ after the first dose |

# 7 STUDY MATERIALS

## 7.1 Study Treatment(s)

### 7.1.1 Study Treatment(s)/ Formulation(s)

- Brimonidine tartrate 0.025% / ketotifen fumarate 0.035% combination ophthalmic solution (n = 334)
- Vehicle ophthalmic solution (n = 167)

### 7.1.2 Instructions for Use and Administration

At Visit 1, a trained study technician will observe the subject, subject's caregiver, or subject's parent/legal guardian (if applicable, for subjects less than 18 years of age) instill investigational drug into each eye according to the directions for use. The subjects enrolled to the PK subset will receive 1 drop of the assigned IP into each eye from a trained technician. At home dosing will begin the morning following Visit 1.

At home, subjects, subject's caregiver, or subject's parent/legal guardian (if applicable, for subjects less than 18 years of age), will instill 1 drop of the assigned investigational drug in each eye BID 7.5 hours apart for up to 6 consecutive weeks (until the evening prior to Visit 4). Subjects must remove contact lenses before instillation of investigational drug and wait at least 10 minutes before reinserting contact lenses.

At Visits 2 and 3, a trained study technician will instill investigational drug in-office 7.5 hours from the previous or following at-home dose.

The final dose of investigational drug will be the dose administered at-home the evening prior to Visit 4.

Subjects will be dispensed two study kits, each containing 2 bottles of assigned IP. Kit 1 will be dispensed at Visit 1. The subject will bring Kit 1 to Visit 2 for in-office installation and kit 1 will be returned to the subject for continued use until Visit 3. Kit 1 will be collected at Visit 3. Kit 2 will be dispensed at Visit 3 and collected at Visit 4.

All bottles of active and vehicle treatment will be identical in appearance and will be packaged in identical containers. The investigational drug kits and each bottle will have a label bearing information meeting applicable regulatory requirements. Investigational drug bottles will come with directions for use and other appropriate information on each

part. Investigational drug will be packaged and labeled based on the randomization list generated prior to the start of the study. Investigational product must be stored at room temperature at 15-25°C (59-77°F).

### 7.2 Other Study Supplies

- Pregnancy tests (Clarity HCG, RAC Medical Boca Raton, FL)
- The ocular anesthetic agent (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP) and dilating drops used for the IOP and dilated Fundoscopy
- Supplies needed for vital signs and physical examination will be provided by Ora, Inc.
- Blood draw supplies (for site participating in pharmacokinetic blood draws) will be supplied by BioAgilytix, the PK Lab vendor.

## 8 STUDY METHODS AND PROCEDURES

### 8.1 Subject Entry Procedures

#### 8.1.1 Overview

Subjects as defined by the criteria in sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

#### 8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject and/or subject's parents/legal guardian, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). Failure to obtain a signed ICF renders the subject ineligible for the study.

In the event that a subject has a medical condition, medication washout, or needs to speak with the Investigator, subject should be scheduled for a Screening Visit, at which time the subject will be given an informed consent form.

#### 8.1.3 Washout Intervals

Medications

Subjects will adhere to the following medication washout intervals during the period indicated **prior to Visit 1** and will refrain from using these medications during the study:

5 days

- artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular corticosteroids, ocular antihistamines, and any other topical ophthalmic agents;

14 days

- any systemic medications which the investigator feels may confound study data or interfere with subject's study participation.

Contact Lenses

Contact lens use is allowed for the duration of the study, but subjects are required to discontinue contact lens use for a period of at least 24 hours prior to each Visit (Visits 1 through 4). Additionally, subjects must remove contact lenses before instillation of study drug at home and wait at least 10 minutes before reinserting contact lenses.

### 8.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion criteria and none of the exclusion criteria in order to be enrolled in the study.

### 8.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the study who sign an ICF will be assigned a subject number that will be entered in the Screening and Enrollment Log. The subject number will consist of the three (3) digit site number, followed by the three (3) digit unique subject identifier, starting with 001.

Once a subject meets all qualification criteria at Visit 1, he/she will be randomized to brimonidine tartrate 0.025%/ ketotifen fumarate 0.035% combination ophthalmic solution or Vehicle in a 2:1 ratio. Each subject who is randomized will be assigned a unique Randomization number in the Randomization and Trial Supply Management (RTSM). Randomization numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. Randomization numbers will be 5 digits and will be created in the RTSM. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across the RTSM treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

## 8.2 **Concurrent Therapies**

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

### 8.2.1 Prohibited Medications/Treatments

Refer to Section 8.1.3 for a complete list of washout periods for the following prohibited medications and treatments:

- artificial tears
- eye whiteners (e.g., vasoconstrictors)
- ocular decongestants
- ocular corticosteroids

- ocular antihistamines
- any other topical ophthalmic agents

8.2.2 Contact Lens Use

Contact lens use is allowed for the duration of the study, but subjects are required to discontinue contact lens use for a period of at least 24 hours prior to each Visit (Visits 1 through 4). Additionally, subjects must remove contact lenses before instillation of study drug at home and wait at least 10 minutes before reinserting contact lenses.

8.2.3 Special Diet or Activities

Not Applicable.

8.3 **Examination Procedures**

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objective(s)

**8.3.1.1 Screening Visit (Day -28 to Day 1)[1]: Screening/ Informed Consent**

- 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/or subject's parent/legal guardian. Subjects wishing to participate must give written informed consent and sign a HIPAA form.

  Prior to randomization at Visit 1, if it is determined the subject did not in fact meet certain criteria, the subject may be brought back at a later date to re-attempt the screening process once the proper washout or timeframes have been achieved. Subjects who re-attempt the screening process within the protocol window will not be given a new subject number. Subjects who re-attempt screening after washout has been met but it falls outside of the protocol window will be given a new subject number.

- Demographic data and medical/medication/ocular and non-ocular history: Collect and record all demographic data, medical history, any medications, and any underlying condition(s). Current underlying conditions, including those that began within the last 30 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 60 days prior to Visit 1.
- Review of Inclusion/Exclusion Criteria: A review of protocol inclusion and exclusion criteria will be confirmed for each subject.
- Adverse Event Query
- Schedule Visit 1: Qualifying subjects will be scheduled to return to the office for Visit 1.

[1] Screening Visit and Visit 1 may be conducted on the same day.

#### 8.3.1.2 VISIT 1 (Day 1): Baseline Assessments, Enrollment/Randomization, and In-Office Instillation[1]

- Update of Medical/Ocular & Non-Ocular History/Medication History
- Adverse Event Query
- Urine Pregnancy Test (for females of childbearing potential): Females of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an acceptable method of contraception throughout participation in the study. For premenarchal subjects, the premenarchal status will be collected.
- Vital Signs: Resting blood pressure and pulse will be collected to exclude subjects that have an abnormal blood pressure. For adult subjects, this is defined as ≤ 90 or ≥ 160 (systolic) measured in mmHg or ≤ 60 or ≥ 100 (diastolic) measured in mmHg. For pediatric subjects, abnormal blood pressure is defined as ≥ 140 (systolic) measured in mmHg or ≥ 90 (diastolic) measured in mmHg.
- Physical Exam: General health, head, eyes, ears, nose, throat (HEENT), and other comments.
- Body Weight: For subjects ≤ 12 years of age, the investigator will compare the subject's body weight to the table in Appendix 4 to determine if the subject's body weight falls above the 5$^{th}$ percentile body weight for their age group. If not, the subject will not be enrolled. For selected subjects agreeing to undergo PK blood draws, the body mass index (BMI) must be ≥18 and ≤34 lbs/in$^2$ and a minimum body weight of 99 lbs.
- BCVA Utilizing an ETDRS Chart: Subjects must have a score of 0.3 logMAR or better in each eye in order to qualify. This initial VA will be deemed the Baseline VA. The use of correction will be documented. If a subject uses correction at this VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score. A clinically significant VA decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event. Please refer to Appendix 2 for details.
- Slit Lamp Biomicroscopy (Pre-Instillation): A slit lamp examination 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, as applicable.

[1] If Screening and Visit 1 are conducted on the same day, Informed Consent/HIPAA, Demographic data and medical/medication/ocular and non-ocular history will be collected at the start of the combined visit.

- Intraocular Pressure (10 years of age or older): An IOP measurement will be performed to exclude subjects with IOP less than 5 mmHg or greater than 22 mmHg.
- Dilated Fundoscopy: A dilated fundus examination will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology. Findings should be recorded as Medical History, as applicable.
- Review of Applicable Inclusion/Exclusion Criteria: The investigator will verify staff member's review of inclusion/exclusion criteria.
- Enrollment /Randomization: Qualifying subjects will be assigned a randomization number and randomized to receive either brimonidine tartrate 0.035%/ketotifen fumarate 0.035% combination ophthalmic solution or vehicle.
- In-Office Investigational Drug Instillation: The RTSM will assign an investigational drug kit number to the subject. A trained study technician will observe the subject, subject's caregiver, or subject's parent/legal guardian (if applicable for subject's less than 18 years of age) instill investigational drug according to the directions for use. The investigational drug kit number and the time of instillation will be recorded. The subjects enrolled to the PK study will receive 1 drop of the assigned IP into each eye from a trained technician.
- Drop Comfort Assessment: Subjects ≥10 years old will assess drop comfort immediately upon instillation, at 30 seconds, and at 1-minute post-instillation [redacted]
- PK Blood Draws (for a subset of 25 healthy adult subjects): Taken pre-IP instillation (within 1 hour prior to dosing), and at 0.25 (± 3 min) hour, 0.5 (± 5 min) hour, 1 (± 10 min) hours, 2 (± 10 min) hours, and 4 (± 20 min) hours after investigational drug instillation.
- Slit Lamp Biomicroscopy (Post-Instillation): A slit-lamp exam will be performed approximately 15 minutes (+3 minutes) after investigational drug instillation. For the subset of healthy adult subjects undergoing PK blood draws, this slit-lamp exam will be conducted after the 0.25 hour draw and prior to the 0.5 hour draw.
- Dispense Investigational Drug and Dosing Diary Dispensation: Enrolled subjects (or subject's caregiver or parent/legal guardian, if applicable) will be instructed to instill 1 drop of investigational drug in each eye, 2 times daily 7.5 hours apart for up to 6 weeks beginning the next morning. Subjects will be instructed on how to complete and record the dosing time in their daily diary. For pediatric subjects, subject's caregiver or subject's parent/legal guardian can provide response to questions, if applicable.

  Subjects, subjects' caregiver or parent/legal guardian (if applicable for subjects less than 18 years of age) will be instructed NOT to dose within 7.5 hours the day of their next scheduled study visit (Visit 2). They will also be instructed to bring

both investigational drug and the daily diary to the next visit (Visit 2) for a compliance check.

- Adverse Event Query
- Schedule Visit 2: Subjects will be asked to return to the office for Visit 2.

#### 8.3.1.3 VISIT 2 (Day 8 ± 2): Follow-up

- Update of Medical/Medication History: Changes to medical history from baseline should be recorded as AEs.
- Adverse Event Query
- Investigational Drug and Dosing Diary Review and Collection: Investigational drug will be collected for re-dispense at the end of the visit. Dosing diary will be collected and reviewed for compliance and to address any queries.
- Urine Pregnancy Test: This will be given to females who were premenarchal at the previous visit (Visit 1) and became menarchal thereafter.
- BCVA Utilizing an ETDRS Chart: If a subject used correction at the baseline VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score. A clinically significant VA decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event. Please refer to Appendix 2 for details.
- Slit Lamp Biomicroscopy (Pre-Instillation)
- In-Office Investigational Drug Instillation: The subject is instructed to return with dispensed kit from Visit 1. A trained study technician will instill investigational drug at least 7.5 hours from previous at-home dose, and according to the directions for use. The investigational drug kit number and the time of instillation will be recorded.
- Drop Comfort Assessment: Subjects ≥10 years old will assess drop comfort immediately upon instillation, at 30 seconds, and at 1-minute post-instillation [redacted]
- Slit Lamp Biomicroscopy (Post-Instillation): A slit-lamp exam will be performed approximately 15 minutes (+3 minutes) after investigational drug instillation.
- Dispense Investigational Drug and Dosing Diary Dispensation: Subjects, subject's caregiver or parent/legal guardian (if applicable for subjects less than 18 years of age) will be re-dispensed the same kit from Visit 1 and instructed to continue their at-home dosing 7.5 hours following their in-office dose, if they haven't completed 2 doses that day already. Subjects will continue to instill 1 drop of investigational drug in each eye, 2 times daily 7.5 hours apart. Subjects will continue to complete

their daily diary as instructed. For pediatric subjects, subject's caregiver or subject's parent/legal guardian can provide response to questions, if applicable.

Subjects (or subjects' caregiver or parent/legal guardian) will be instructed NOT to dose within 7.5 hours the day of their next scheduled study visit (Visit 3). They will also be instructed to bring both investigational drug and the daily diary to the next visit (Visit 3) for a compliance check.

- Adverse Event Query
- Schedule for Visit 3: Subjects will be asked to return to the office for Visit 3

#### 8.3.1.4 VISIT 3 (Day 22 ± 3): Follow-up

- Update of Medical/Medication History: Changes to medical history from baseline should be recorded as AEs.
- Adverse Event Query
- Investigational Drug and Dosing Diary Review and Collection: Investigational Drug and Dosing diary will be collected and reviewed for compliance and to address any queries.
- Urine Pregnancy Test: This will be given to females who were premenarchal at the previous visit (Visit 2) and became menarchal thereafter.
- BCVA Utilizing an ETDRS Chart: If a subject used correction at the baseline VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score. A clinically significant VA decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event. Please refer to Appendix 2 for details.
- Slit Lamp Biomicroscopy (Pre-Instillation)
- In-Office Investigational Drug Instillation: The RTSM will assign an investigational drug kit number to the subject. A trained study technician will instill investigational drug at least 7.5 hours from previous at-home dose, and according to the directions for use. The investigational drug kit number and the time of instillation will be recorded.
- Drop Comfort Assessment: Subjects ≥10 years old will assess drop comfort immediately upon instillation, at 30 seconds, and at 1-minute post-instillation [redacted]
- PK Blood Draws (for the same subset of 25 healthy adult subjects): Taken pre-IP instillation (within 1 hour prior to dosing), and at 0.25 (± 3 min) hour, 0.5 (± 5 min) hour, 1 (± 10 min) hours, 2 (± 10 min) hours, and 4 (± 20 min) hours after investigational drug instillation.

- Slit Lamp Biomicroscopy (Post-Instillation): A slit-lamp exam will be performed approximately 15 minutes (+3 minutes) after investigational drug instillation. For the subset of healthy adult subjects undergoing PK blood draws, this slit-lamp exam will be conducted after the 0.25 hour draw and prior to the 0.5 hour draw.
- Dispense Investigational Drug and Dosing Diary Dispensation: Subjects, subject's caregiver or parent/legal guardian (if applicable for subjects less than 18 years of age) will be instructed to continue their at-home dosing 7.5 hours following their in-office dose, if they haven't completed 2 doses that day already.

  Subjects will continue to instill 1 drop of investigational drug in each eye, 2 times daily 7.5 hours apart. Subjects (or subjects' caregiver or parent/legal guardian) will be instructed NOT to dose on the day of their next scheduled study visit (Visit 4). The last dose for this study will be instilled at-home the day prior to the next visit (Visit 4). They will also be instructed to bring both investigational drug and the daily diary to the next visit (Visit 4) for a compliance check.
- Adverse Event Query
- Schedule for Visit 4: Subjects will be asked to return to the office for Visit 4

#### 8.3.1.5 VISIT 4 (Day 43 + 3): Treatment Discontinuation and Exit Visit

- Update of Medical/Medication History: Changes to medical history from baseline should be recorded as AEs.
- Adverse Event Query
- Investigational Drug and Dosing Diary Review and Collection: Investigational Drug and Dosing diary will be collected and reviewed for compliance and to address any queries
- Urine Pregnancy Test: This will be given to all females of childbearing potential
- Vital Signs: Resting blood pressure and pulse
- Physical Exam: General health, head, eyes, ears, nose, throat, and other comments
- BCVA Utilizing an ETDRS Chart: If a subject used correction at the baseline VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score. A clinically significant VA decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event. Please refer to Appendix 2 for details.
- Slit Lamp Biomicroscopy
- Intraocular Pressure (should be performed on subjects 10 years of age or older)
- Dilated Fundoscopy

- Adverse Event Query
- Study Exit: Subjects will be exited from the study.

Adverse Events (AEs) (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate eCRF.

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. 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 Ora.

## 8.4 Schedule of Visits, Measurements and Dosing

### 8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

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

If a subject is discontinued at a scheduled study visit, the remaining assessments should be captured on the Unscheduled Visit/Early Exit Visit pages of the Source Document and corresponding eCRF.

### 8.4.2 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 to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit/ Early Exit Visit pages of the Source Document and corresponding eCRF.

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit), include but are not limited to:

- Update of Medical/Medication History
- Assessment of Adverse Events
- BCVA Utilizing an ETDRS chart: If a subject used correction at the baseline VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score.
- Urine Pregnancy Test (for females of childbearing potential)
- Slit Lamp Biomicroscopy

- Vital Signs (resting blood pressure and pulse)
- Physical Examination
- Intraocular Pressure (should be performed on subjects ≥10 years old)
- Dilated Fundoscopy

8.4.3 Exit Procedures

For exit or early termination on subjects that are enrolled, the reason for exiting should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

Exit procedures should be performed to ensure subject safety. All information gathered at the final visit should be recorded on the Unscheduled Visit pages of the Source Document and corresponding eCRF.

Evaluations that may be conducted as part of study Exit (as appropriate, depending on the reason for the visit), include but are not limited to:

- Update of Medical/Medication History
- Assessment of Adverse Events
- BCVA Utilizing an ETDRS chart: If a subject used correction at the baseline VA then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years old who are developmentally unable to use the ETDRS chart, a best attempt at VA will be made using the LEA symbols or Visual Behavior. For subjects utilizing LEA symbols, Snellen equivalent units of 20/63 or better in both eyes will be required. Subjects utilizing Visual Behavior must have a passing score.
- Urine Pregnancy Test (for females of childbearing potential)
- Slit Lamp Biomicroscopy
- Vital Signs (resting blood pressure and pulse)
- Physical Examination
- Intraocular Pressure (should be performed on subjects ≥10 years old)
- Dilated Fundoscopy

The exit visit need not be a separate visit. If a subject disqualifies during a scheduled visit, the above evaluations should be recorded on the Unscheduled Visit of the Source Document and corresponding eCRF.

## 8.5 Compliance with Protocol

Subjects who are inappropriately enrolled may be discontinued from the study. The reason for such discontinuation will be recorded as “protocol violation” in the source document and on the appropriate page in the eCRF.

Site staff will review concomitant medication use at each visit. Any new medication (or) changes in existing concomitant medication use will be recorded in the source document and on the Concomitant medication eCRF.

## 8.6 Subject Disposition

### 8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

### 8.6.2 Discontinued Subjects

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

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- Investigator decision
- sponsor termination of study
- other

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible, and to retrieve all study materials. Whenever possible, discontinued subjects should be followed through the last scheduled study visit. Subject withdrawals will be documented clearly on the source document and applicable eCRF.

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 sponsor and will be clearly documented on the eCRF.

## 8.7 Lost to Follow-up

Subjects who do not return for their scheduled visits as defined by the visit window and cannot be contacted, may be considered lost to follow-up. Attempts to contact the subjects should include at least 2 phone calls, emails and/or text messages and a certified letter. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed. For subjects that are lost to follow-up, the date of early termination will be the date of the last attended clinic visit and the date of last dose will be the date of the last in-office instillation.

## 8.8 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or Ora with appropriate notification.

## 8.9 Study Duration

This trial consists of 4-5 office visits over a period of approximately 6 to 10 weeks.

### 8.10 Monitoring and Quality Assurance

During the course of the study an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora quality assurance and/or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

## 9 ADVERSE EVENTS

### 9.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject participating in a clinical study, which does not necessarily have a causal relationship with the study product/procedure. Therefore, an adverse event includes:

- Any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease onset, that occurs at any time between the signing of the ICF and study exit, without any judgement about causality (i.e., whether or not it is considered to be related to the study product)
- Exacerbation, worsening, or progression of a pre-existing illness, including an increase in severity, frequency, and/or duration of a pre-existing episodic event or condition
- Events occurring from drug overdose (accidental or intentional), drug abuse or misuse, drug hypersensitivity, drug extravasation, drug interactions, drug dependency, events occurring from drug withdrawal and medication errors
- A condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following administration of study drug.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).

Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE.

### 9.1.1 Assessment of Severity of Adverse Events

The severity of an AE will be graded as follows:

| | |
|---|---|
| Mild | Awareness of a sign or symptom but is easily tolerated, requires no treatment, and does not interfere with subject's daily activities |
| Moderate | Low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care |
| Severe | Interrupts the subject's daily activity and requires systemic therapy or other treatment |

### 9.1.2 Assessment of Causality of Adverse Events

The relationship of an AE to the study product will be assessed using the following guidelines, based upon available information:

| | |
|---|---|
| Related | There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. |
| Not Related | There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists. |

Rationale MUST be provided for any "not related" assessment and is recommended for "related" assessments.

## 9.2 Serious Adverse Events

An AE is considered "serious" if it meets at least one of the following criteria. The event:

- Results in death
- Is life threatening (places the subject at immediate risk of death)

  NOTE: The term "life-threatening" in the definition of "serious" 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 inpatient hospitalization or prolongation of existing hospitalization
  NOTE: The term "hospitalization" refers to admission to a hospital as an in-patient for more than 24 hours. Therefore, an adverse event would meet the SAE criterion of "requires hospitalization" only if the event necessitated admission to a

health care facility for longer than 24 hours. Elective hospitalization for an intervention that was already planned before inclusion of the subject in the study, hospitalization solely for the purpose of diagnostic tests (even if related to an AE), hospital admission for social circumstances, and admission to a day-care facility may not constitute sufficient grounds to be considered an SAE.

Cases in which subjects are retained in the emergency room for more than 24 hours but not admitted for medical care should be evaluated individually, because the criterion "otherwise medically significant" may apply (see below).

- Results in persistent or significant disability/incapacity

  NOTE: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance (e.g., uncomplicated headache, influenza, or sprained ankle) that may transiently interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect

- Is considered otherwise medically significant, as determined by the PI or medically qualified sub-investigator

  NOTE: The term "medically significant" refers to important medical events that may not immediately be life threatening or result in death or hospitalization, but, based upon appropriate medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE.

  Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Spontaneous abortion, elective abortion and ectopic pregnancy will be considered SAEs and must be reported to the sponsor within 24 hours of awareness of the event.

Subjects will be withdrawn from the study if an SAE is identified and thought to be related to the study drug.

The investigator is responsible for the reporting of all SAEs.

Within 24 hours following the investigator's knowledge of an SAE, the investigator must:

- Report the SAE to the sponsor/designee.

  All SAEs occurring between screening and 30 days after the last administered dose of study drug (inclusive) must be reported to the sponsor/designee, independent of the circumstance or suspected cause, and regardless of the relationship to the study drug or protocol, within 24 hours from the time the event was reported to the investigator. For events occurring beyond the 30-day period after the last application of study drug, or for any timeframe greater than 30 days

deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the sponsor.

If the subject dies during participation in the study or during recognized follow-up period, and if cause of death is not available within the 24-hour reporting period, "death" must be reported as an SAE term to meet the timelines. Cause of death must be actively queried and submitted as a follow-up report.

- Fax or email a completed Serious Adverse Event Report to the following designees:

**Sponsor Contact:**

[redacted]

**Contract Research Organization Contact:**

[redacted]

Include copies of all confirmatory examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the subject's identity is protected (personal identifiers are redacted), and the date and subject identifier in the clinical trial (i.e., subject number) are clearly visible on every page/copy of source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.

- Investigators should not wait to receive additional information before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required.

**Within 48 hours** following the investigator's knowledge of an SAE, the investigator must:

- Enter the information related to the SAE in the appropriate sections of the eCRF.
- Send notification of the SAE to the monitoring team after investigator approval of the eCRF.

All further data updates should be recorded in the CRF within one working day of knowledge of this additional information. Send notification of the updated SAE information to the monitoring team after investigator approval of the eCRF.

Additional documentation (e.g., laboratory data, concomitant medication, subject status, etc.), should be sent by fax or e-mail to the monitoring team within one working day of knowledge of this information. Care should be taken to ensure that the subject's identity is protected (personal identifiers are redacted) and the date and subject identifier in the clinical trial (i.e., subject number) are clearly visible on every page/copy of source document that is provided to the monitoring team. For laboratory results, include the laboratory normal ranges.

After the end of study visit, the investigator does not need to actively monitor subjects for new SAEs. However, if the investigator becomes aware of a new or previously unreported serious adverse event within 30 days after the last investigational drug instillation, the event should be reported to the sponsor/designee within 24 hours of learning of the event. If the investigator becomes aware of a new or previously unreported SAE after 30 days from the last investigational drug instillation, only SAEs considered related to the study drug should be reported to the sponsor within 24 hours of the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial SAE Report Form cases for the purposes of expedited reporting.

### 9.2.1 Expedited Serious Adverse Events

Any suspected unexpected serious adverse event considered related to the study drug may warrant expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or related to the conduct of the study), regardless of whether or not the study drug was administered, will be evaluated by Global Pharmacovigilance and Risk Management to determine if expedited reporting is required. For example, an unexpected, severe SAE that could be associated with the study procedures and could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form Food and Drug Administration (FDA) 3500A, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study medical monitor. Once the report is compiled, the study center's investigator must submit the expedited safety report to the local IRB/IEC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The principal investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB/IEC. It is important that the principal investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

### 9.2.2 Pregnancy

All female subjects of childbearing potential and male subjects with female partners of childbearing potential must use at least 1 medically acceptable form of birth control throughout the study duration, for at least 14 days prior to (Visit 1) and 1 month after discontinuing the IP, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method. Before enrolling a female subject of childbearing potential or a male subject with a female partner of childbearing potential, the investigator must review the following information about study participation:

- Informed consent requirement
- Contraceptives in current use

By signing the informed consent form, the investigator or designee asserts that he/she has discussed this information with the subject and provided appropriate counseling. Following the review of this information, the subject must sign the informed consent

form to enroll in the study. During the study, all subjects should be instructed to contact the investigator immediately if they suspect that they or their partners might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to randomization, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject is considered to be a screen failure, must not continue in the study, and must not receive study drug. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued, and the subject and neonate will be followed until 30 days after the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, both when pregnancy is confirmed, and 30 days after the delivery date. Information provided on the Pregnancy Report Form must include the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

If a subject is withdrawn from the study and is found to be pregnant within 30 days of withdrawal, the subject and neonate will be followed until 30 days after the pregnancy comes to term.

All confirmed pregnancies must be immediately reported to the sponsor/designee and medical monitor on a Pregnancy Report form within 24 hours of the investigator's awareness of the pregnancy. If a pregnancy is associated with an SAE, an SAE report form should also be submitted to the sponsor/designee and medical monitor within 24 hours of the investigator's awareness. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Completed SAE Report Forms and completed Pregnancy Report Forms should be transmitted to the sponsor/designee and the medical monitor using the contact information provided in Section 9.2 above.

If/when the investigator becomes aware of any new information regarding a pregnancy, the sponsor/designee and medical monitor should be notified of these updates as soon as the new information becomes available. Updates should be documented on a Pregnancy Report Form and sent by fax or email using the contact information provided above. The report should be marked as a follow-up report" and should include the updated status of the pregnancy. The original Pregnancy Report Form is not to be altered.

## 9.3 General Guidelines for Reporting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the course of the study. Throughout the study, efforts will be made by the investigator to remain alert to possible AEs. The period of observation for collection of AEs extends from the time the subject gives informed consent until the last study visit or discontinuation from the study. The first concern will always be the safety of the subject, and appropriate medical intervention will be made.

The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit. Each AE which appears to be independent of any prior event will be reported separately.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject, will be recorded. Any AEs deemed related to treatment reported or observed at the final study/treatment visit will be followed until stabilization or resolution (or up to 30 days after final study visit).

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Tolerability signs and symptoms that result in the subject's requiring a concomitant therapy, interruption of treatment, or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment/therapy, if given
- Outcome
- Resolution

The investigator will also provide an assessment of the causal relationship to the study drug (for pre-treatment AEs, causality is "not related"). Rationale MUST be provided for any "not related" assessment and is recommended for "related" assessments.

All AEs must be reported regardless of whether the AEs are considered drug-related.

In order to ensure the safety of the subjects, the investigator should take appropriate measures to follow all subjects with adverse events until clinical recovery is complete, progression has been stabilized, the subject is lost to follow-up, or until death. This may result in the need for observations to continue beyond the last planned protocol specified visit, and additional investigations may be requested by the monitoring team.

If a subject requires further follow-up of ongoing AEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary.

Laboratory results, vital signs, or electrocardiogram (ECG) abnormalities are to be recorded as AEs (or SAEs, if applicable) only if at least one of the following apply:

- the result is clinically significant

- the subject is symptomatic
- the subject requires either corrective treatment or consultation
- the lab result, vital sign, or ECG abnormality leads to study drug discontinuation or dose modification
- the event fulfills a criterion for an SAE

In addition, the investigator's assessment of causality will be recorded.

Vital sign abnormalities are to be recorded as AEs (or SAEs, if applicable) only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

Site staff will provide subjects with the main office number plus a 24-hour number to report any adverse events or safety concerns. This information will be listed on the Informed Consent Form and a copy will be provided to the subject at their Screening Visit or Visit 1 (if Screening and Visit 1 are done on the same day).

### 9.4 Procedures for Unmasking (if applicable)

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the sponsor should be notified before unmasking IP.

## 10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

### 10.1 Study Populations

Safety Population: The safety population includes all subjects who have received at least one dose of study medication. All safety and tolerability parameters will be analyzed using the safety population and using the treatment that subjects actually received.

Pharmacokinetic (PK) Population: The PK population includes all enrolled subjects who provide at least one blood sample drawn post-dose.

### 10.2 Unit of Analysis

For tolerability and non-ocular safety analyses, the unit of analysis will be the subject (in the case of assessments that are recorded for each eye, the average of the eyes will be used). For the ocular safety analyses, the unit of analysis will be each eye.

### 10.3 Primary Statistical Hypothesis

Statistical hypotheses will not be tested in this safety study.

### 10.4 Sample Size

501 subjects will be randomized yielding approximately 334 subjects randomized to brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution and 167 subjects randomized to vehicle. Three-hundred thirty-four actively treated subjects yield at least 95% probability of detecting AEs that occur at a rate of 1% or greater.

Of the subject total, approximately 100 pediatric subjects are anticipated to be enrolled into this study.

### 10.5 Demographic and Baseline Characteristics

Subject demographics: gender, race, ethnicity, and iris color will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics.

### 10.6 Safety Analysis

The following safety variables will be recorded. All safety analyses will be repeated on the age subgroups - 5-12 years old, 13-17 years old, 18-64 years old, and for ages greater than 64 years.

- Adverse Events (AEs; reported, elicited and observed)
- Urine Pregnancy Test
- Best- Corrected Visual Acuity using an ETDRS chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure (should be performed on subjects ≥ 10 years old)
- Physical Examination
- Vital Signs (resting blood pressure and pulse)
- Dilated Fundus Examination

All safety parameters will be analyzed on the Safety Population. The results of VA, slit lamp biomicroscopy, IOP, vital signs will be presented by treatment and visit with numerical summaries. Change from baseline will also be presented in the same manner.

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and lid will be performed at each visit. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

The observed and change from baseline VA will be summarized for each eye (study eye and non-study eye) using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects.

The results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline.

Dilated Fundus Examination results will be summarized using counts and percentages for each treatment group and for all actively treated subjects at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the dilated fundoscopy parameters will also be provided comparing each follow-up visit to baseline.

Physical examination results, graded as normal or abnormal, will be summarized by treatment group and for all actively treated subjects using counts and percentages at each visit (including a summary of baseline values). Change from baseline will also be summarized to each post-baseline visit using counts and percentages.

Vital signs will be summarized with continuous descriptive statistics at each day (including a summary of baseline values) and time point by treatment group and for all actively treated subjects. Change from baseline will also be summarized to each post-baseline visit. Additionally, for each measure, a worst-case low and worst-case high post-baseline value and change from baseline value will be presented.

Height, weight, and BMI will be summarized for a subset of subjects using continuous descriptive statistics at each day (including a summary of baseline values) and time point by treatment group and for all actively treated subjects. Change from baseline will also be summarized to each post-baseline visit. Additionally, for each measure, a worst-case low and worst-case high post-baseline value and change from baseline value will be presented.

### 10.7 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequencies and percentages of TEAEs will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature treatment discontinuation by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs.

### 10.8 Dosing Compliance and Extent of Exposure

A subject who has taken at least 80% but not greater than 120% of the scheduled doses will be considered as study drug compliant. Compliance for all treated subjects will be summarized with descriptive statistics by treatment group. Counts and percentages of compliant subjects (80% - 120%), non-compliant subjects (<80%), and over compliant subjects (>120%) will be summarized. Extent of exposure, defined as number of days each subject was on the study drug will be summarized with descriptive statistics.

Subgroup analyses by age group (5 years – 12 years), (13 years – 17 years), (18 years – 39 years), (40 years – 64 years), and (65 years and up) will be performed as appropriate on necessary safety parameters, including summaries of IOP, VA, slit lamp biomicroscope, and Dilated fundoscopy.

### 10.9 Tolerability Analysis

Brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution will be compared to vehicle for the tolerability parameter of drop comfort using 2-sample t-tests for each assessment time point. Subgroup analyses by age group (5 years – 12 years), (13 years – 17 years), (18 years – 39 years), (40 years – 64 years), and (65 years and up) will be performed.

### 10.10 Pharmacokinetics Analysis

Plasma concentrations of brimonidine and ketotifen by scheduled time point will be summarized using descriptive statistics: n, mean, median, standard deviation (SD), minimum, maximum, and percent coefficient of variation (% CV).

Where data allow, the PK parameters ($C_{max}$, $C_{min}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-4h}$, $R_{Cmax}$, and $R_{AUC}$) for brimonidine and ketotifen will be obtained using standard non-compartmental methods. PK parameters will be summarized using descriptive statistics by day: n, mean, median, SD, minimum, maximum, and % CV.

Concentration values reported as below the limit of quantitation (BLQ) before the first quantifiable concentration or after the last quantifiable concentration will be set to zero for concentration descriptive statistics and PK analyses. If a concentration that is BLQ is imbedded between 2 measurable concentrations, the BLQ value will be set to missing.

Figures will be created to display mean and individual subject concentration-time curves in plasma.

Additional PK analyses may be performed at the Sponsor's discretion during or at the conclusion of the study.

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

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IP in the countries involved will be adhered to.

### 11.1 Protection of Human Subjects

#### 11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the 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 amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

#### 11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations (CFR) Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/IEC approved version of the informed consent form will be used.

### 11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

### 11.3 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 that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the FDA, the Department of Health and Human Services (DHHS), other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

### 11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and ECGs. The investigator's copy of the CRFs serves as the investigator's record of a subject's study-related data.

#### 11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will

accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

## 11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

### 11.5.1 Labeling/Packaging

The investigational materials will be packaged and labeled in a manner consistent with the study design. They will be labelled according to the local regulatory requirements.

Subjects will be dispensed two kits containing 2 bottles of assigned IP each. Kit 1 will be dispensed at Visit 1. The subject will bring Kit 1 to Visit 2 for in-office installation and kit 1 will be returned to the subject for continued use until Visit 3. Kit 1 will be collected at Visit 3. Kit 2 will be dispensed at Visit 3 and collected at Visit 4.

### 11.5.2 Storage of Investigational Product

The IP must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

IP must be stored at room temperature at 15-25°C (59-77°F).

### 11.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s) and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the sponsor on the Product Accountability Log.

### 11.5.4 Return or Disposal of Investigational Product

All IP will be returned to the sponsor at the end of the study.

## 11.6 Recording of Data on Source Documents and Case Reports Forms (CRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's CRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

## 11.7 Handling of Biological Specimens

See Appendix 7 'Blood Collection, Handling, and Shipment for Pharmacokinetic Analysis for details.

## 11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the sponsor will have the final decision regarding the manuscript and publication.

## 12 REFERENCES

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# 13 APPENDICES

## APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

| Assessments Performed | Screening | Visit 1 (Baseline) | Visit 2 | Visit 3 | Visit 4 |
|---|---|---|---|---|---|
| | Day -28 to Day 1 | Day 1 | Day 8 ± 2 | Day 22 ± 3 | Day 43 + 3 |
| Informed Consent/Assent/HIPAA[1] | X | | | | |
| Demographics | X | | | | |
| Medical/Medication/Ocular/Non-Ocular History | X | | | | |
| Medical and Medication History Update | | X | X | X | X |
| Review of Inclusion/Exclusion Criteria | X | X | | | |
| Urine Pregnancy Test[2] | | X | X | X | X |
| Visual Acuity[5] | | X | X | X | X |
| Slit Lamp Biomicroscopy[6] | | X | X | X | X |
| Intraocular Pressure[7] | | X | | | X |
| Vital Signs (Resting Blood Pressure and Pulse) | | X | | | X |
| Physical Exam[4] | | X | | | X |
| Body Weight Determination (PK subjects) (subjects ≤12 years of age)[3] | | X | | | |
| Dilated Fundoscopy | | X | | | X |
| Enrollment/Randomization | | X | | | |
| In-Office Investigational Drug Instillation | | X[8] | X | X | |
| Drop Comfort Assessment[9] | | X | X | X | |
| PK blood draw[10] | | X | | X | |
| Dispense Investigational Drug | | X | X[11] | X | |
| Dispense Dosing Diary[12] | | X | X | X | |
| Collection of Returned Investigational Drug & Dosing Diary | | X | X | X | X |
| Assessment of Adverse Events | X | X | X | X | X |
| Exit | | | | | X |

1. Assent is to be taken from subjects who are at least 7 years of age and less than 18 years of age. Informed consent and/or Assent must be signed before any study-related procedure can be performed. If washout of certain medications is necessary, informed consent must be obtained at Screening Visit.
2. To be conducted on females of childbearing potential. At Visits 2 and 3, a urine pregnancy test will be conducted for females who were premenarchal at the previous visit and became menarchal thereafter.

3. The Investigator will refer to Appendix 4 for subjects ≤12 years of age only.
4. Physical Examination includes general health, head, eyes, ears, nose, throat (HEENT), and any other comments.
5. If a subject used correction at the baseline visit then they should use the same correction throughout all subsequent VA assessments. For subjects under 10 years of age who are developmentally unable to use ETDRS chart, a best attempt at obtaining VA will be made by using a LEA symbols VA chart (measured as Snellen equivalent units). If subject requires Visual Behavior, they must have a passing score.
6. Evaluated prior to and 15 minutes (+ 3 minutes) post IP instillation at Visits 1-3, and once at Visit 4.
7. Age ≥ 10 years old.
8. Subjects and/or subject's parent/legal guardian will instill IP at Visit 1 and will be observed by a trained study technician. The subjects enrolled to the PK study will receive 1 drop of the assigned IP into each eye from a trained technician.
9. Subjects ≥ 10 years old will assess comfort immediately upon instillation, at 30 seconds, and at 1-minute post-instillation using a [redacted] for each eye. Subjects < 10 years old will not assess drop comfort.
10. (for subjects agreeing to undergo PK blood draws) Pre-dose (within 1 hour prior to dosing) and at 0.25 (±3 min) hour, 0.5 (±5 min) hour, 1 (±10 min) hour, 2 (±10 min) hours, and 4 (±20 min) hours after the first study drug administration in the morning on Day 1 and on Day 22.
11. A new kit is dispensed at Visit 1 and Visit 3. At Visit 2, the kit that was dispensed at Visit 1 is re-dispensed for dosing until Visit 3.
12. A new dosing diary will be distributed at Visits 1, 2, and 3.

# APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

## Visual Acuity Procedures (ETDRS Chart)

LogMAR visual acuity (VA) must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. VA should be evaluated at the beginning of each visit in the study (i.e., prior to slit-lamp examination). VA testing should be done with most recent correction.

Equipment

The VA chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use either Series 2000 Chart 1 or Chart 2 or chart 'R', and the right eye should be tested first. The chart should remain the same for all visits at the site. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (e.g., that was a "C" not an "O") before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

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 1 of 2 letters, he or she should be asked to choose 1 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 x 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 VA 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 |

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of VA during the study, all VA assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a subject forgets his glasses), the reason for the change in correction should be documented.

**LEA Symbols Visual Acuity (for subjects under the age of 10 if necessary):**

Visual acuity testing is to be performed in the same manner at each visit. The LEA symbols visual acuity chart should be used for subjects under the age of 10 when necessary.

Mark a spot on the floor (e.g. with tape) that is 10 feet (3 meters) from the bottom of the wall with the eye chart. The test distance and illumination for the chart must be kept constant throughout the study.

First establish a method of communication such as naming (signing) or pointing (matching). Decide with the child which names will be used to identify the symbols.

Briefly point to the first symbol in each line in descending order when testing binocularly. Do not leave the pointer close to the symbol because it makes fixation easier, especially in case of amblyopia, lazy eye. If the child seems to have difficulties in knowing which line to look at, cover the line above the line to be read with a white card leaving a little of the upper line visible.

Move down until the child hesitates or misidentifies a symbol.

Move back up one line and ask the child to identify all the symbols on that line.

If the child identifies all symbols correctly go to the next line with smaller symbols and ask the child to identify all the symbols on that line.

If the child skips a symbol ask the child to try again while briefly pointing to that symbol.

A child with an amblyopic eye may typically skip symbols within a line of symbols.

Visual acuity is recorded as the last line on which at least 3 of the 5 symbols are identified correctly.

When tested 3 meters (10 feet), the visual acuity value is found in the margin adjacent to that line. Subjects utilizing LEA symbols must have Snellen equivalent units of 20/63 to qualify.

After obtaining good responses with binocular testing, proceed by testing each eye separately.

When testing monocularly, use the first symbol of each line or every second line for one eye and the last symbol of each line for the other eye to determine on which line to start testing.

Age-appropriate visual acuity test will be performed. For subjects under the age of 10, when LEA Symbols cannot be assessed, the clinician may use an alternative method to evaluate visual acuity. Visual Behavior (fix and follow, wince and no wince) will be used in children unable to be tested with the Snellen chart. Every effort should be made to obtain a VA measurement in children. The same VA testing method is to be employed for all study visits for each subject. Visual Behavior is graded as a pass/fail test.

**Pregnancy Testing**

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

**Dilated Fundoscopy**

Dilated fundus exams will be performed using indirect ophthalmoscopy at Visit 1 (Day 1) and Visit 4 (Day 43 +3). 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 study 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.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes (subject) should be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

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.

**Intraocular Pressure**

Applanation tonometry, Goldmann tonometer required. Do NOT use non-contact tonometry. It is recommended that Fluress® (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP) be used as the anesthetic. It is recommended that subjects should wait a minimum of 10 minutes after instillation of Fluress® before instilling investigational drug.

IOP should always be measured/recorded before pupil dilation.

[redacted]

[redacted]

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

[redacted]

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

**Vital Signs**

Each subject will have vital signs assessments (resting blood pressure and pulse) conducted at Visits 1 and 4 (if enrolled). Vital signs are to be conducted by qualified staff member who may be any of the following: a Board-certified Investigator or sub-Investigator, Nurse Practitioner, Registered Nurse, or Physician's Assistant.

- **Pulse (bpm)**

  Pulse will be measured with the subjects who have been in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds and multiplied by 2, and recorded in beats per minute.

  It is recommended that pediatric subject's pulse should not be:

  - < 60 (lower than 60) bpm or >130 (higher than 130) if subject is between the ages of 5 and 11
  - <50 (lower than 50) bpm or >120 (higher than 120) if subject is between the ages of 12 and 17

- **Systolic/ Diastolic Blood Pressure (mmHg)**

  Systolic and diastolic blood pressure should be measured in the same arm each time using a sphygmomanometer with the subjects who have been in a resting state (seated upright) at least 5 minutes. Blood pressure will be recorded in mm Hg.

**Body Weight**

Body weight will be measured for subjects ≤ 12 years of age and PK subjects on Visit 1. Body weight is to be measured by qualified staff member who may be any of the following: a Board-certified Investigator or sub-Investigator, Nurse Practitioner, Registered Nurse, or Physician's Assistant.

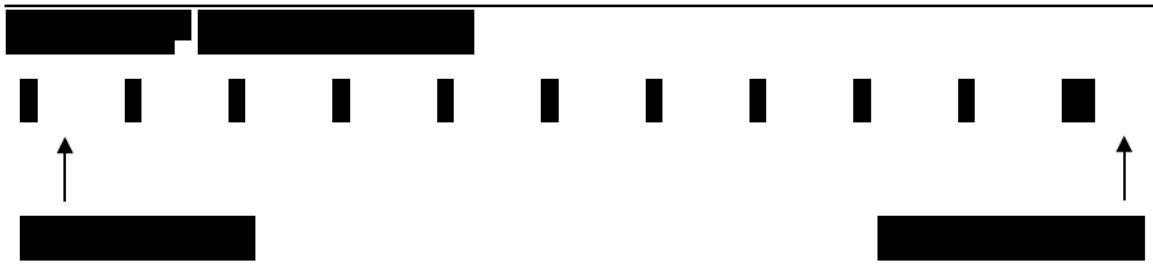
**Physical Examination**

Each subject will have a physical examination conducted at Visit 1 and Visit 4 (if enrolled). A physical examination may be conducted by a Board-certified Investigator or sub-Investigator, Nurse Practitioner or Physician's Assistant. The physical examination will also include an assessment of the following:

- General health
- Head, Eyes, Ears, Nose, Throat (HEENT)
- Comments

**Subject-Reported Drop Comfort**:

Subjects that are at least 10 years of age will assess drop comfort for each eye immediately upon instillation, and at 30 seconds, and at 1 minute following in-office dosing using the [redacted] Scale:



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

## APPENDIX 3: SUBJECT DOSING DIARIES

**Sample Dosing Diary Instructions:**
**Visits 1-2 and 2-3 Dosing Diary**

**Subject Initials: _____** **Subject Number: _____**

**DOSING INSTRUCTIONS**

- Please dose **ONE** (1) drop in each eye with the study drops **TWO** (2) times a day 7.5 hours apart, starting the morning after your Visit 1 appointment. Below is an example of a dosing schedule:
    - Dose 1 (8:00AM)
    - Dose 2 approximately 8 hours after Dose 1 (4:00PM)

  ****DO NOT** dose any earlier than 7.5 hours after your previous dose****

- Circle **YES** if dose was taken or check **NO** if dose was not taken
- Be sure to record what time you took your dose in your diary
- Please complete dosing up to your next scheduled visit, **DO NOT** dose within 7.5 hours of your next appointment.

Principal Investigator Name: _____

24-hr phone number: _____

**Visit ____ Appointment:**

**Date:_____**

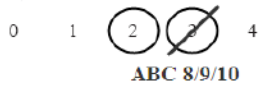
**Time:_____**

**APPENDIX 3 (Continued)**

**Subject Initials: _____ Subject Number: _____**

**GENERAL INSTRUCTIONS**

- Use a **black pen** to fill out your diary. **DO NOT** use white-out or pencil.
- Enter the date for each day, in the following format: DD/MMM/YYYY.
  **For example, January 10th, 2023 would be written as 10/JAN/2023.**
- If you make an error, draw a **SINGLE LINE** through the error, and then **DATE** and **INITIAL** below the line. Then enter the correct value or score.




- You should keep your investigational drug bottles at room temperature (15-25° [59-77°F]). Keep the bottles out of sunlight, and do not freeze or refrigerate the investigational drug. Please keep the bottle tightly closed when not in use. Keep away from children.
- Wash your hands thoroughly before using the study drops.
- To prevent contamination of the bottle and solution, do not touch the tip of the bottle to your eye, eyelids, surrounding areas or other surfaces.
- Look up and gently pull down the lower eye lid with one hand. With your other hand, hold the bottle upside down over each target eye, and slowly squeeze 1 drop onto the lower surface of each eye. Gently close your eye and allow the drop to be absorbed. **DO NOT** squeeze your eyelids shut.
- If you wear contact lenses, you must remove them before instillation of study drug and wait at least 10 minutes before reinserting contact lenses.
- For pediatric subjects, subject's caregiver or subject's parent/legal guardian can provide response to questions, if applicable.
- You **MUST** bring back your completed diary and investigational drug with you to your next visit.

**APPENDIX 3 (Continued)**

Sample Dosing Diary:

**Subject Initials: _____** **Subject Number: _____**

**Date: ___ ___/ ___ ___ ___/ 2023**

D D M M M

| | | |
|---|---|---|
| **DOSE 1** | Was the dose taken? | Yes No |
| | Time dose taken: | ___ ___:___ ___ **(24 Hour Clock)** |

| | | |
|---|---|---|
| **DOSE 2** | Was the dose taken? | Yes No |
| | Time dose taken: | ___ ___:___ ___ **(24 Hour Clock)** |

***Use Black Ink pen ONLY***

**APPENDIX 3 (Continued)**

**Sample Dosing Diary Instructions:**
**Visits 3-4 Dosing Diary**

**Subject Initials: _____** **Subject Number: _____**

**DOSING INSTRUCTIONS**

- Please continue to dose **ONE** (1) drop in each eye with the study drops **TWO** (2) times a day 7.5 hours apart. Below is an example of a dosing schedule:
    - Dose 1 (8:00AM)
    - Dose 2 approximately 8 hours after Dose 1 (4:00PM)

  ****DO NOT** dose any earlier than 7.5 hours from your previous dose****

- Circle **YES** if dose was taken or check **NO** if dose was not taken
- Be sure to record what time you took your dose in your diary
- Please complete dosing up to your next scheduled visit, **DO NOT** dose the day of your next appointment (Visit 4).

Principal Investigator Name: _____

24-hr phone number: _____

**Visit 4 Appointment:**

**Date:_____**

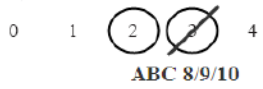
**Time:_____**

**APPENDIX 3 (Continued)**

**Subject Initials: _____ Subject Number: _____**

**GENERAL INSTRUCTIONS**

- Use a **black pen** to fill out your diary. **DO NOT** use white-out or pencil.
- Enter the date for each day, in the following format: DD/MMM/YYYY.
  **For example, January 10th, 2023 would be written as 10/JAN/2023.**
- If you make an error, draw a **SINGLE LINE** through the error, and then **DATE** and **INITIAL** below the line. Then enter the correct value or score.



ABC 8/9/10

- You should keep your investigational drug bottles at room temperature (15-25° [59-77°F]). Keep the bottles out of sunlight, and do not freeze or refrigerate the investigational drug. Please keep the bottle tightly closed when not in use. Keep away from children.
- Wash your hands thoroughly before using the study drops.
- To prevent contamination of the bottle and solution, do not touch the tip of the bottle to your eye, eyelids, surrounding areas or other surfaces.
- Look up and gently pull down the lower eye lid with one hand. With your other hand, hold the bottle upside down over each target eye, and slowly squeeze 1 drop onto the lower surface of each eye. Gently close your eye and allow the drop to be absorbed. **DO NOT** squeeze your eyelids shut.
- If you wear contact lenses, you must remove them before instillation of study drug and wait at least 10 minutes before reinserting contact lenses
- For pediatric subjects, subject's caregiver or subject's parent/legal guardian can provide response to questions, if applicable.
- You **MUST** bring back your completed diary and investigational drug with you to your next visit (Visit 4).

**APPENDIX 3 (Continued)**

Sample Dosing Diary:

**Subject Initials: _____** **Subject Number: _____**

**Date: ___ ___/ ___ ___ ___/ 2023**

D D M M M

| | | |
|---|---|---|
| **DOSE 1** | Was the dose taken? | Yes No |
| | Time dose taken: | ___ ___:___ ___ **(24 Hour Clock)** |

| | | |
|---|---|---|
| **DOSE 2** | Was the dose taken? | Yes No |
| | Time dose taken: | ___ ___:___ ___ **(24 Hour Clock)** |

***Use Black Ink pen ONLY***

# APPENDIX 4: TABLE OF FIFTH (5TH) PERCENTILE BODY WEIGHTS BY AGE

| **Age in years** | **Sex** | **5TH Percentile Body Weight** | |
|---|---|---|---|
| | | Kg | Lb |
| **5** | Boys | 15.23 | 33.58 |
| | Girls | 14.71 | 32.43 |
| **6** | Boys | 16.93 | 37.32 |
| | Girls | 16.44 | 36.24 |
| **7** | Boys | 18.74 | 41.31 |
| | Girls | 18.23 | 40.19 |
| **8** | Boys | 20.66 | 45.55 |
| | Girls | 20.15 | 44.42 |
| **9** | Boys | 22.71 | 50.07 |
| | Girls | 22.32 | 49.21 |
| **10** | Boys | 24.93 | 54.96 |
| | Girls | 24.87 | 54.83 |
| **11** | Boys | 27.50 | 60.63 |
| | Girls | 27.84 | 61.38 |
| **12** | Boys | 30.55 | 67.35 |
| | Girls | 31.15 | 68.67 |

http://www.cdc.gov/growthcharts/html_charts/wtage.htm

Centers for Disease Control and Prevention, National Center for Health Statistics August 24, 2001

## APPENDIX 5: PROTOCOL AMENDMENTS

| Section | Page | Description of Change | Rationale |
|---|---|---|---|

## APPENDIX 6: XANTHINE-CONTAINING BEVERAGES AND PRODUCTS

| | |
|---|---|
| **Coffee:** | All methods of preparation: drip, percolate, espresso, etc., instant or ground, regular or decaffeinated. Commercially prepared coffees (e.g., Café Vienna, Café Francais, etc.) |
| **Tea:** | All forms: regular, green, black, orange, pekoe, oolong. All methods of preparation: steeped, brewed, sun tea, iced tea, instant or brewed, loose or bagged teas, decaffeinated teas. |
| **Soft Drinks:** | All dark sodas and some lighter sodas- regular, diet, and sugar free:<br>• Coke/Pepsi<br>• RC Cola<br>• Orange/Slice<br>• Mr. Pibb<br>• Tab<br>• Mountain Dew<br>• Dr. Pepper<br>• Chocolate Soda<br>• Root Beer |
| **Milk:** | Milk products containing chocolate (chocolate shakes, malts, ice-cream, and cocoa) |
| **Bottled Water:** | Aqua Joe |
| **Baked Goods:** | Chocolate baked goods, such as Devil's Food cakes, chocolate chip cookies, Oreo or sandwich type cookies, chocolate custards, frostings, icings, etc. |
| **Snacks or Treats:** | Any chocolate containing desserts (mousse, puddings, yogurts, mocha products, etc.) or candies covered with or containing chocolate. |

## APPENDIX 7: BLOOD COLLECTION, HANDLING, AND SHIPMENT FOR PHARMACOKINETIC ANALYSIS

See separate Lab Manual for PK blood collection, handling, and shipment details.

## APPENDIX 8: SPONSOR APPROVALS

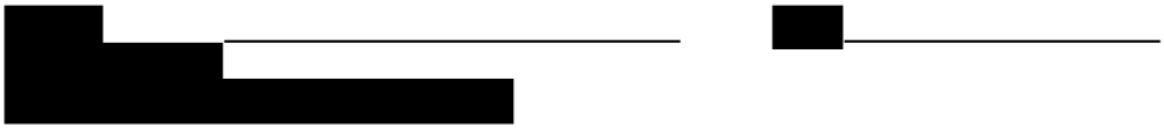
| | |
|---|---|
| **Protocol Title:** | A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Pharmacokinetics of Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution, Used Two Times Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis) |
| **Protocol Number:** | 913/22-100-0006 |
| **Final Date:** | 07 Jul 2023 |

[redacted]

## APPENDIX 9: ORA APPROVALS

| | |
|---|---|
| **Protocol Title:** | A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Pharmacokinetics of Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution, Used Two Times Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis) |
| **Protocol Number:** | 913/22-100-0006 |
| **Final Date:** | 07 Jul 2023 |

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.



## APPENDIX 10: INVESTIGATOR'S SIGNATURE

| | |
|---|---|
| **Protocol Title:** | A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Pharmacokinetics of Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Combination Ophthalmic Solution, Used Two Times Daily in Healthy Adult Subjects and in Pediatric Subjects with a History or Family History of Atopic Disease (including Allergic Conjunctivitis) |
| **Protocol Number:** | 913/22-100-0006 |
| **Final Date:** | 07 Jul 2023 |

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address> Specify address and phone number for each study location.
<enter phone number>