Clinical Trial Protocol: 909

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model
Protocol Number:	909
Study Phase:	3
Investigational Product Name:	Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution (Combo)
IND Number:	153035
Indication:	Allergic Conjunctivitis
Investigators:	Multi-Center
Sponsor:	Bausch & Lomb Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, Third Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673

	Date
Original Protocol (v1.0):	15Jun2022
Amendment 1 (v2.0):	23 Aug 22
Amendment 2 (v3.0):	02 Dec 22
Amendment 3 (v4.0):	03 Apr 23

Confidentiality Statement

SPONSOR PERSONNEL

Sponsor:	Bausch & Lomb Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Sponsor Representative:	[redacted]

ORA PERSONNEL

Department Vice President:	[redacted]
Project Manager:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model
Protocol Number:	909
Investigational Product:	Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution (Combo)
Study Phase:	3
Primary Objective(s):	To evaluate the efficacy of Combo compared to its individual components and vehicle in a population of subjects with allergic conjunctivitis.
Secondary Objective(s):	Not Applicable.
Overall Study Design:	
Structure:	The study will consist of 6 study visits: a Screening Period of 3 study visits to verify subjects are eligible to participate and, following randomization, a Treatment Period of 3 study visits to evaluate the onset of action and potential for an 8 hour duration of effectiveness for the brimonidine tartrate/ ketotifen fumarate Combo drug product compared to its individual components and vehicle. *Screening Period:* At Visit 1, subjects will sign the informed consent form (ICF) and an allergic skin test will be performed, if required. At Visit 2, subjects will undergo an ocular allergen challenge titration using an allergen that elicited a positive reaction via skin testing. Subjects with a positive reaction post-Conjunctival Allergen Challenge (CAC) will undergo a confirmation CAC at Visit 3 with the same allergen qualified during Visit 2. *Treatment Period:* Treatment will begin at Visit 4a after subjects are randomized 1:1:1:1 to receive

	either brimonidine tartrate 0.025%/ketotifen fumarate 0.035% ophthalmic solution (Combo) bilaterally, ketotifen fumarate 0.035% bilaterally, brimonidine tartrate 0.025% bilaterally, or vehicle ophthalmic solution bilaterally. At this visit, subjects will receive an in-office dose of the treatment they were randomized to receive. Approximately 8 hours post-instillation of study medication, at Visit 4b, subjects will undergo a CAC. Subjects will receive a final dose of study medication at Visit 5 approximately 15 minutes prior to CAC at that visit. Efficacy evaluations will be conducted at Visit 4b and Visit 5.
Duration:	This trial consists of 6 office visits over a period of approximately 5 to 10 weeks.
Controls:	• Ketotifen fumarate ophthalmic solution 0.035% • Brimonidine tartrate ophthalmic solution 0.025% • Vehicle ophthalmic solution
Dosage Instillation:	At Visit 4a, a trained study technician will instill 1 drop of the assigned investigational product into each eye approximately 8 hours (+1 hour) prior to the Visit 4b CAC. At Visit 5, a trained study technician will instill 1 drop of the assigned investigational product into each eye approximately 15 minutes (+1 minute) prior to the Visit 5 CAC.
Summary of Visit Schedule:	**Visit 1 (Day -52 to Day -22):** Screening / Informed Consent / Skin Test **Visit 2 (Day -21 ± 3):** Titration CAC **Visit 3 (Day -14 ± 3):** Confirmation CAC **Visit 4a (Day 1):** Enrollment / Randomization / In-Office Instillation **Visit 4b (8 hours from Visit 4a):** 8 Hour Duration of Action CAC

	Visit 5 (Day 15 ± 3): In-Office Instillation / 15-Minute Onset of Action CAC
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to investigational product, 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 180 subjects, 45 subjects per treatment group, will be enrolled.
Condition/Disease:	Allergic Conjunctivitis
Inclusion Criteria:	Subjects must: 1. be at least 10 years of age of either sex and any race; 2. provide written informed consent and sign a HIPAA form. Subjects who are under the age of 18 will need to sign an assent form as well as having a parent or legal guardian sign an informed consent; 3. be willing and able to follow all instructions and attend all study visits; 4. (If female and of childbearing potential) agree to have urine pregnancy testing performed at visits 2, 4a (must be negative) and at exit visit (Visit 5); must not be lactating; and must agree to use at least 1 medically acceptable form of birth control throughout the study duration, for at least 14 days prior to the first dose of investigational drug (Visit 4a) and for 1 month after the last dose of investigational drug (Visit 5). 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 4a). 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); 5. (If male and with female partner 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 the first dose of investigational drug (Visit 4a) and for 1 month after the last dose of the study drug (Visit 5) 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 the first dose of investigational drug (Visit 4a). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository; 6. have a history of ocular allergies and a positive skin test reaction to a seasonal (grass, ragweed, tree pollen) or perennial (cat dander, dog dander, dust mites, cockroach) allergen as confirmed by an allergic skin test conducted at Visit 1 or within the past 24 months; 7. have a calculated best-corrected visual acuity of 0.7 LogMar or better in each eye as measured using an ETDRS chart at Visit 2; 8. have a positive bilateral CAC reaction (defined as having scores of ≥ 2 for ocular itching and ≥ 2 for conjunctival redness) within 10 minutes of instillation of the last titration of allergen at Visit 2;

	9. have a positive bilateral CAC reaction (defined as having scores of ≥ 2 for ocular itching and ≥ 2 for conjunctival redness) in at least 2 out of 3 timepoints at following the challenge at Visit 3; 10. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study trial period.
Exclusion Criteria:	Subjects may <u>not</u>: 1. have known contraindications or sensitivities to the use of any of the investigational product(s) or their components; 2. have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium, or a diagnosis of dry eye); 3. have had ocular surgical intervention within 3 months prior to enrollment (Visit 4a) and/or a history of refractive surgery within 6 months prior to enrollment (Visit 4a); 4. have a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease; 5. have the presence of an active ocular infection (bacterial, viral or fungal), positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit; 6. manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 2, 3, or 4a (defined as a score of >0 for itching and/or >1 for conjunctival redness); 7. use any of the following disallowed medications during the period indicated prior to Visit 2 and agree not to use disallowed medications throughout the study: **<u>7 Days</u>**

	systemic or ocular H_1 antihistamines, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine-vasoconstrictor drug combinations, • decongestants, • immunotherapeutic agents, • monoamine oxidase inhibitors, • artificial tears, • eye whiteners (eg, vasoconstrictors), • lid scrubs, • mast cell stabilizers, • prostaglandins or prostaglandin derivatives, • ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs); **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.* **14 Days** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **45 Days** • depo-corticosteroids **2 Months** • immunosuppressive or cancer chemotherapeutic agents *Note: Currently marketed over-the-counter anti-allergy eyedrops (i.e., anti-histamine/vasoconstrictor combination products like Visine-A® or Naphcon-A®) may be administered to subjects at the end of each visit, after all evaluations are completed*; 8. have any significant illness (for example, any autoimmune disease requiring therapy, or severe cardiovascular disease [including arrhythmias]) the Investigator feels could be expected to interfere with the subject's safety or study parameters and/or put the

	subject at any unnecessary risk (includes but is not limited to poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens); 9. have planned surgery (ocular or systemic) during or within 30 days after the trial period; 10. have used an investigational drug or device within 30 days of the study or be concurrently enrolled in another investigational drug or device study within 30 days of the study; 11. be a female who is currently pregnant, planning a pregnancy, or lactating; 12. have a history of glaucoma, ocular hypertension or have an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg in either eye at Visit 2. 13. Have symptoms associated with COVID-19 or have been in contact with someone diagnosed with COVID-19 within the last 14 days of the Screening Visit 14. Have been randomized in the Bausch & Lomb 910 study.
Study Formulations and Formulation Numbers:	**Test Article:** Brimonidine tartrate 0.025%/ketotifen fumarate 0.035% combination ophthalmic solution (Combo), [redacted] **Active Control #1**: Ketotifen fumarate 0.035% ophthalmic solution , containing benzalkonium chloride, glycerin, mannitol, povidone, and water for injection. Hydrochloric acid and/or sodium hydroxide may be used to adjust pH.

	Active Control #2: Brimonidine tartrate 0.025% ophthalmic solution, containing benzalkonium chloride, glycerin, mannitol, povidone, and water for injection. Hydrochloric acid and/or sodium hydroxide may be used to adjust pH. **Vehicle Control:** Vehicle ophthalmic solution, containing benzalkonium chloride, glycerin, mannitol, povidone, and water for injection. Hydrochloric acid and/or sodium hydroxide may be used to adjust pH.
Evaluation Criteria:	
Efficacy Measures and Endpoints:	**Primary Efficacy Measures** • Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5 • Conjunctival redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5 **Secondary Efficacy Measures** • Ciliary redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5 • Episcleral redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5 **Exploratory Efficacy Measures** • Eyelid swelling score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, not allowing half unit increments) at Visits 4b and 5 • Tearing score (average score of the subject's two eyes) evaluated by the subject

	at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5 • Chemosis score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5 • Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5
Safety Measures:	• Adverse Events (AEs; reported, elicited and observed) • Best-corrected VA at Distance Utilizing an ETDRS chart • Slit-lamp Biomicroscopy • IOP • Dilated Fundoscopy
Tolerability Measures:	• Ocular comfort grade (lowest score of the subject's two eyes) assessed by the subject upon investigational product instillation and at 1 minute (± 0.5 minutes) after investigational product instillation at Visit 4a (0-10 unit scale) • Subject description of drop comfort questionnaire assessed at 3 minutes post-instillation at Visit 4a
General Statistical Methods and Types of Analyses Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. Analysis Populations Intent to Treat (ITT) Set: The ITT set will consist of all randomized subjects who are instilled with study drug. The ITT population will be analyzed as randomized. Full Analysis Set (FAS): The FAS will consist of all randomized subjects who are instilled with study drug and have at least one post-instillation of IP assessment of both primary endpoints. The FAS population will be analyzed as randomized.	

Per Protocol Set (PP Set): The PP Set will consist of FAS subjects with no protocol violations considered to affect the evaluability of efficacy, as determined through masked review of deviations prior to unmasking. The PP population will be analyzed as treated.

Safety Set: The Safety Set will include all subjects who receive any amount of study medication. The safety population will be analyzed as treated.

Safety Analysis

The number and percentage of subjects with specific treatment-emergent adverse events (AEs) will be summarized for each treatment group. The number of subjects will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Visual acuity, biomicroscopy findings, IOP, and dilated fundoscopy will be summarized descriptively.

Primary Efficacy Analyses

Statistical success will be achieved if all of the following conditions are met at Visits 4b for duration of action and Visit 5 for onset of action.

The Combo is superior in ocular itching and ocular redness to Vehicle.

The Combo is superior in ocular itching to brimonidine tartrate 0.025%.

The Combo is superior in ocular redness to ketotifen fumarate 0.035%.

Superiority will be demonstrated for the first bullet point above if all of the following are true.

- For each endpoint, the estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and vehicle) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- For each endpoint, the estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- For each endpoint at each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided $\alpha = 0.0125=0.025/2$ to account for the two timepoints) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the timepoints, then the third time point is tested at the unused one-sided alpha of 0.0125.

Superiority will be demonstrated for the second and third bullet points above if all of the following are true.

- The estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and the comparator) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- The estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- At each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided $\alpha = 0.0125=0.025/2$ to account for the two timepoints) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the timepoints, then the third time point is tested at the unused one-sided alpha of 0.0125.

Hypotheses

Superiority Tests

For each primary endpoint at each of the six evaluation times, four superiority hypotheses will be tested comparing the Combo to a comparator (ketotifen fumarate 0.035%, brimonidine tartrate 0.025% or Vehicle). The null hypothesis (H_0) is that the mean score for the subjects in the test (Combo) group (μ_T) is greater than or equal to the mean score for the subjects in the comparator group (μ_C). The alternative hypothesis (H_1) is that the mean score for the subjects in the test group is less than the mean score for the subjects in the comparator group.

$$H_0: \mu_T \geq \mu_C$$

$$H_1: \mu_T < \mu_C$$

Methods

Each primary endpoint will be summarized by post-CAC timepoint at each visit by treatment group using continuous summary statistics and analyzed using an ANCOVA model with terms for baseline value and treatment for the ITT population. Missing data will be imputed using multiple imputation methods. Least square means for each treatment group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals.

Tolerability Analysis

The lowest ocular comfort score of each subject's two eyes at each assessment time will be used in the analysis. Comfort scores will be summarized using continuous summary statistics by treatment, visit, and time.

Sample Size Calculations

A sample size of 40 subjects in each treatment group will have at least 98% power to detect a difference in means of 1 unit at each time point assuming that the common standard deviation is 1 unit using a two-group t-test with a 1.25% one-sided significance level. Given that both efficacy measures (itching and redness) must pass in order to declare success, the overall power is at least 96%. To allow for 10% dropouts, 45 subjects will be randomized in each of the treatment groups.

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
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
DHHS	Department of Health and Human Services
ECG	electrocardiogram
eCRF	electronic case report form
ERB	ethical review board
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPC	giant papillary conjunctivitis
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug application
IOP	Intraocular pressure
IP	investigational product
IRB	institutional review board
ISAAC	International Study of Asthma and Allergies in Childhood
ITT	intent to treat
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
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PAC	perennial allergic conjunctivitis
PHI	protected health information
PO	by mouth
PP	per protocol
PRN	as needed
RTSM	Randomization and Trial Supply Management
SAC	seasonal allergic conjunctivitis
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
T_{max}	time of maximum concentration
USP	United States Pharmacopeia
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 (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 still remains an unmet need specifically for patients affected by more chronic forms of ocular allergy.

The purpose of this study is to evaluate the efficacy of Brimonidine Tartrate 0.025%/ Ketotifen Fumarate 0.035% Ophthalmic Solution (Combo) compared to its individual components in a population of subjects with 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 Combo is intended to utilize the unique attributes of each active agent to reduce ocular itching and redness for up 8 hours.

2 STUDY OBJECTIVES

The primary objective is to evaluate the efficacy of Combo compared to its individual components and vehicle in a population of subjects with allergic conjunctivitis.

3 CLINICAL HYPOTHESES

It is hypothesized that Combo will be more efficacious than its individual components and vehicle in a population of subjects with allergic conjunctivitis.

4 OVERALL STUDY DESIGN

This is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled study.

The study will consist of 6 study visits: a Screening Period of 3 study visits to verify subjects are eligible to participate and, following randomization, a Treatment Period of 3 study visits to evaluate the onset of action and potential for an 8 hour duration of effectiveness for the brimonidine tartrate/ketotifen fumarate Combo drug product compared to its individual components and vehicle.

At Visit 1, subjects will sign the informed consent form (ICF) and an allergic skin test will be performed, if required. At Visit 2, subjects will undergo an ocular allergen challenge titration using an allergen that elicited a positive reaction via skin testing. Subjects with a positive reaction post-CAC will undergo a confirmation CAC at Visit 3 with the same allergen qualified during Visit 2.

Treatment will begin at Visit 4a after subjects are randomized 1:1:1:1 to receive either brimonidine tartrate 0.025%/ketotifen fumarate 0.035% ophthalmic solution (Combo) bilaterally, ketotifen fumarate 0.035% ophthalmic solution bilaterally, brimonidine tartrate 0.025% ophthalmic solution bilaterally, or vehicle ophthalmic solution bilaterally. At this visit, subjects will receive an in-office dose of the treatment they were randomized to receive. Approximately 8 hours post-instillation of study medication, at Visit 4b, subjects will undergo a CAC. Subjects will receive a final dose of study medication at Visit 5 approximately 15 minutes prior to CAC. Efficacy evaluations will be conducted at Visit 4b and Visit 5.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 180 subjects, 45 subjects per treatment group, will be enrolled.

5.2 Study Population Characteristics

Subjects of at least 10 years of age of either sex and any race, with a diagnosis of allergic conjunctivitis, who meet all of the inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects must:

1. be at least 10 years of age of either sex and any race;
2. provide written informed consent and sign a HIPAA form. Subjects who are under the age of 18 will need to sign an assent form as well as having a parent or legal guardian sign an informed consent;
3. be willing and able to follow all instructions and attend all study visits;
4. (If female and of childbearing potential) agree to have urine pregnancy testing performed at visits 2, 4a (must be negative) and at exit visit (Visit 5); must not be lactating; and must agree to use at least 1 medically acceptable form of birth control throughout the study duration, for at least 14 days prior to the first dose of investigational drug (Visit 4a) and for 1 month after the last dose of investigational drug (Visit 5). 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 4a). 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);
5. (If male and with female partner 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 the first dose of investigational drug (Visit 4a) and for 1 month after the last dose of the study drug (Visit 5) 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 the first dose of investigational drug (Visit 4a). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository;
6. have a history of ocular allergies and a positive skin test reaction to a seasonal (grass, ragweed, tree pollen) or perennial (cat dander, dog dander, dust mites,

cockroach) allergen as confirmed by an allergic skin test conducted at Visit 1 or within the past 24 months;

7. have a calculated best-corrected visual acuity of 0.7 LogMar or better in each eye as measured using an ETDRS chart at Visit 2;
8. have a positive bilateral CAC reaction (defined as having scores of ≥ 2 for ocular itching and ≥ 2 for conjunctival redness) within 10 minutes of instillation of the last titration of allergen at Visit 2;
9. have a positive bilateral CAC reaction (defined as having scores of ≥ 2 for ocular itching and ≥ 2 for conjunctival redness) in at least 2 out of 3 timepoints at following the challenge at Visit 3;
10. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study trial period.

5.4 Exclusion Criteria

Exclusion Criteria:

Subjects may <u>not</u>:

1. have known contraindications or sensitivities to the use of any of the investigational product(s) or their components;
2. have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium, or a diagnosis of dry eye);
3. have had ocular surgical intervention within 3 months prior to enrollment (Visit 4a) and/or a history of refractive surgery within 6 months prior to enrollment (Visit 4a);
4. have a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease;
5. have the presence of an active ocular infection (bacterial, viral or fungal), positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit;
6. manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 2, 3, or 4a (defined as a score of >0 for itching and/or >1 for conjunctival redness);
7. use any of the following disallowed medications during the period indicated prior to Visit 2 and agree not to use disallowed medications throughout the study:

   <u>7 Days</u>

   - systemic or ocular H_1 antihistamines, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine-vasoconstrictor drug combinations,
   - decongestants,
   - immunotherapeutic agents,

- monoamine oxidase inhibitors,
- artificial tears,
- eye whiteners (eg, vasoconstrictors),
- lid scrubs,
- mast cell stabilizers,
- prostaglandins or prostaglandin derivatives,
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);
  **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.*

14 Days

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

45 Days

- depo-corticosteroids

2 Months

- immunosuppressive or cancer chemotherapeutic agents

Note: Currently marketed over-the-counter anti-allergy eyedrops (i.e., anti-histamine/vasoconstrictor combination products like Visine-A® or Naphcon-A®) may be administered to subjects at the end of each visit, after all evaluations are completed;

8. have any significant illness (for example, any autoimmune disease requiring therapy, or severe cardiovascular disease [including arrhythmias]) the Investigator feels could be expected to interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk (includes but is not limited to poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens);
9. have planned surgery (ocular or systemic) during or within 30 days after the trial period;
10. have used an investigational drug or device within 30 days of the study or be concurrently enrolled in another investigational drug or device study within 30 days of the study;
11. be a female who is currently pregnant, planning a pregnancy, or lactating;
12. have a history of glaucoma, ocular hypertension or have an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg in either eye at Visit 2.
13. Have symptoms associated with COVID-19 or have been in contact with someone diagnosed with COVID-19 within the last 14 days of the Screening Visit;
14. Have been randomized in the Bausch & Lomb 910 study.

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 Efficacy Measures and Endpoints

6.1.1 Primary Efficacy Measure(s) and Endpoints

- Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Conjunctival redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

6.1.2 Secondary Efficacy Measure(s) and Endpoints

- Ciliary redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Episcleral redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

6.1.3 Exploratory Efficacy Measure(s) and Endpoints

- Eyelid swelling score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, not allowing half unit increments) at Visits 4b and 5
- Tearing score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5
- Chemosis score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5

6.2 Safety Measures

- Adverse Events (AEs; reported, elicited and observed)

- Best-corrected VA at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- IOP
- Dilated Fundoscopy

6.3 Tolerability Measures

- Ocular comfort grade (lowest score of the subject's two eyes) assessed by the subject upon investigational product instillation and at 1 minute (± 0.5 minutes) after investigational product instillation at Visit 4a (0-10 unit scale)
- Subject description of drop comfort questionnaire assessed at 3 minutes post-instillation at Visit 4a

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 (Combo) (n = 45)
- Ketotifen fumarate ophthalmic solution 0.035% (n = 45)
- Brimonidine tartrate ophthalmic solution 0.025% (n = 45)
- Vehicle ophthalmic solution (n = 45)

7.1.2 Instructions for Use and Administration

- At Visit 4a, a trained study technician will instill 1 drop of the assigned investigational product into each eye approximately 8 hours (+1 hour) prior to the Visit 4b CAC.
- At Visit 5, a trained study technician will instill 1 drop of the assigned investigational product into each eye approximately 15 minutes (+1 minute) prior to the Visit 5 CAC.

7.2 Other Study Supplies

- Pregnancy tests (Clarity HCG RAC Medical Boca Raton, FL)
- Fluress® ocular anesthetic agent (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP) for intraocular pressure
- Dilating drops for dilated fundoscopy

- Allergens used for skin testing and conjunctival allergen challenge (cat dander, dog dander, dust mites, cockroach, individual grasses, ragweed, and individual trees)

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 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/contact lens washout, or needs to speak with the Investigator prior to Visit 1, the subject will be given an informed consent form. Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

8.1.3 Washout Intervals

Subjects will adhere to the following medication washout intervals during the period indicated **prior to Visit 2** and will refrain from using these medications during the study:

72 Hours

- **contact lenses**

7 Days

- systemic or ocular H_1 antihistamines, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine-vasoconstrictor drug combinations,
- decongestants,
- immunotherapeutic agents,
- monoamine oxidase inhibitors,
- artificial tears,
- eye whiteners (eg, vasoconstrictors),
- lid scrubs,

- mast cell stabilizers,
- prostaglandins or prostaglandin derivatives,
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs); **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.*

14 Days

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

45 Days

- depo-corticosteroids

2 Months

- immunosuppressive or cancer chemotherapeutic agents

Note: Currently marketed over-the-counter anti-allergy eyedrops (i.e., anti-histamine/vasoconstrictor combination products like Visine-A® or Naphcon-A®) may be administered to subjects at the end of each visit, after all evaluations are completed.

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 screening number that will be entered in the Screening and Enrollment Log. The screening number will consist of three (3) digits, starting with 001.

Once a subject meets all qualification criteria at Visit 4a, he/she will be randomized to brimonidine tartrate 0.025%/ ketotifen fumarate 0.035% combination ophthalmic solution (Combo), ketotifen fumarate ophthalmic solution 0.035%, brimonidine tartrate ophthalmic solution 0.025%, or Vehicle in a 1:1:1:1 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 of 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:

contact lenses

- systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer drug combinations, H1 antihistamine- vasoconstrictor drug combinations
- decongestants
- immunotherapeutic agents
- monoamine oxidase inhibitors
- artificial tears
- eye whiteners (eg, vasoconstrictors)
- lid scrubs
- mast cell stabilizers
- prostaglandins or prostaglandin derivatives
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs) **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.*
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers
- depot-corticosteroids
- immunosuppressive or cancer chemotherapeutic agents

8.2.2 Escape Medications

Subjects may receive either anti-itch cream or Calamine lotion (depending on the washout) after the skin test has been completed at Visit 1.

Cold compress should first be used in the management of allergic symptoms. Subjects may be prescribed an anti-inflammatory or anti-allergy medication at the Investigator's discretion. Subjects, however, will be discontinued if prescribed such anti-inflammatory or anti-allergy medication.

Currently marketed over-the-counter anti-allergy eye drops (i.e., anti-histamine/ vasoconstrictor combination products such as Visine-A® or Naphcon-A®) may be administered to subjects by trained personnel at the end of Visits 2, 3, 4b, and 5, after all evaluations are completed. Relief drop use at the visits should be recorded on the Concomitant medication log.

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 VISIT 1 (Day -52 to Day -22): Screening/ Informed Consent/ Skin Test

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

  In the event that a subject has a medical condition, medication/contact lens washout, or needs to speak with the Investigator prior to Visit 1, the subject will be given an informed consent form. Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

- *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.

- *Allergic Skin Test, if applicable:* A diagnostic test for allergic disease (skin test) will be performed if there is no documented skin test within the past 24 months. Subjects may receive either anti-itch cream or Calamine lotion (depending on the washout) after the skin test has been completed.

- *Review of Inclusion/Exclusion Criteria:* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

- *Adverse Event Query*

- *Schedule Visit 2:* Qualifying subjects will be scheduled to return to the office for Visit 2.

8.3.1.2 VISIT 2 (Day -21 ± 3): Titration CAC

- *Update of Medical/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.

- *Best-Corrected Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify. This initial visual acuity will be deemed the Baseline visual acuity. The use of correction will be documented. If a subject uses correction at this visual acuity then they should use the same correction throughout all subsequent visual acuity assessments.

- *Slit Lamp Biomicroscopy:* 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.

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular and nasal allergic signs and symptoms using the Ora-CAC® scales. Subjects exhibiting signs or symptoms of clinically active allergic conjunctivitis in either eye (defined as a score of >0 itching and/or >1 conjunctival redness) will be excluded.

- *Review of Inclusion/Exclusion Criteria* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

- *Titration Conjunctival Allergen Challenge (CAC):* A conjunctival allergen challenge (CAC) will be performed bilaterally with a perennial or seasonal allergen serially diluted in buffered saline and administered via a micropipette according to Ora SOPs. One drop of a solubilized allergen to which the subject is sensitized, at the weakest dilution, will be instilled bilaterally into the conjunctival cul-de-sac.

  If the subject fails to react within 10 (±2) minutes, increasingly concentrated doses may be instilled bilaterally at approximately ten-minute intervals until a positive reaction is elicited. If increasing doses are required (i.e., for insufficient bilateral itching and/or redness as evaluated by a trained technician or the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen, other allergens to which the subject is sensitized may be used starting at the lowest dose.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Upon completion of the initial titration CAC, subjects will receive an ocular examination by the Investigator to evaluate all Investigator-evaluated efficacy measures and confirm the subject's qualification. Subjects will be asked to assess their ocular and nasal symptoms.

A positive CAC at Visit 2 is defined as a score of ≥ 2 for redness in the conjunctival vessel bed of each eye and ≥ 2 for itching in each eye within 10 (±2) minutes of receiving that dose of allergen. Assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will also be made at this time by the subject. Assessments of redness (ciliary and episcleral) and chemosis will also be made at this time by the Investigator. Any subject who fails to test positively will be excluded from the study.

Note: The type and concentration of allergen used to elicit a positive reaction will be recorded for each qualifying subject. At all subsequent visits, subjects will receive the same type of allergen (same lot number) and same concentration identified at this visit.

- *Intraocular Pressure:* Intraocular pressure (IOP) will be measured in each eye by contact tonometry. Subjects with an IOP of < 5 mmHg or > 22 mmHg will be excluded.

- *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.

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, over-the-counter anti-allergy eyedrop (i.e., anti-histamine/vasoconstrictor combination products like Visine-A® or Naphcon-A®) by trained study personnel as they leave the office to relieve any immediate discomfort caused by the allergic reaction. Relief drop use should be recorded on the Concomitant medication log.

- *Adverse Event Query*

- *Schedule Visit 3:* Subjects will be asked to return to the office for Visit 3.

8.3.1.3 VISIT 3 (Day -14 ± 3): Confirmation CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart*: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.

- *Slit Lamp Biomicroscopy*

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular and nasal allergic signs

and symptoms using the Ora-CAC® scales. Subjects exhibiting signs or symptoms of clinically active allergic conjunctivitis in either eye (defined as a score of >0 itching and/or >1 conjunctival redness) will be excluded.

- *Review of Inclusion/Exclusion Criteria* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

- *Confirmation CAC*: For each qualified subject, one drop of the allergen solution, of the same, final dose that elicited a positive reaction at Visit 2, will be administered bilaterally.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**). If the subject fails to react positively (i.e., ≥2 ocular itching and ≥2 redness in the conjunctival vessel bed) in both eyes in at least two (2) out of the first three (3) time points[1], he/she will be excluded from the study.

- *Relief Drop Instillation:* Relief drop use should be recorded on the Concomitant medication log.

- *Adverse Event Query*

- *Schedule for Visit 4a:* Subjects will be asked to return to the office for Visit 4a.

8.3.1.4 VISIT 4a (Day 1): Enrollment / Randomization / In-Office Instillation

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (for females of childbearing potential*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.

- *Slit Lamp Biomicroscopy*

- *Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales. Subjects exhibiting signs or symptoms of clinically active

[1] not necessarily at the same time point

allergic conjunctivitis in either eye (defined as a score of >0 itching and/or >1 conjunctival redness) will be excluded.

- *Review of Inclusion/Exclusion Criteria* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

  Enrollment/Randomization: Subjects who meet all of the inclusion criteria and none of the exclusion criteria and qualify to continue in the study will be assigned a sequential Randomization number (5 digits) in the RTSM and randomly assigned to receive either Combo, brimonidine tartrate 0.025%, ketotifen fumarate 0.035%, or Vehicle. Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted.

- *Investigational Product Instillation:* A trained study technician will instill the assigned investigational product according to the directions for use. The time of instillation will be recorded.

- *Drop Comfort Assessment:* Drop comfort will be assessed immediately upon instillation, at 1 minute (± 0.5 minutes) and 2 minutes (± 0.5 minutes) post-instillation (0 – 10 scale).
- *Drop Comfort Descriptor Questionnaire:* The subject will select 3 descriptor terms for drop comfort at 3 minutes post-instillation.

- *Adverse Event Query*

- *Schedule for Visit 4b:* Subjects will be asked to return to the office 7 ½ hours after investigational product instillation. Subjects will be instructed to avoid allergens which may trigger an ocular allergic response.

8.3.1.5 VISIT 4b (8 hours from Visit 4a): 8 Hour Duration of Action CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.

- *Slit Lamp Biomicroscopy*

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular allergic signs and symptoms using the Ora-CAC® scales.

- *8 Hour Duration of Action CAC*: Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2, 8 hours (+1 hour) post-instillation of investigational product at Visit 4a.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**).

- *Relief Drop Instillation:* Relief drop use should be recorded on the Concomitant medication log.

- *Adverse Event Query*

- *Schedule for Visit 5:* Subjects will be asked to return to the office for Visit 5.

8.3.1.6 VISIT 5 (Day 15 ± 3): In-Office Instillation / 15-Minute Onset of Action CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (for females of childbearing potential)*

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess pre-CAC ocular and nasal allergic signs and symptoms using the Ora-CAC® scales. Subjects exhibiting signs or symptoms of clinically active allergic conjunctivitis in either eye (defined as a score of >0 itching and/or >1 conjunctival redness) will be discontinued.

- *Investigational Product Instillation:* A trained study technician will instill the assigned investigational product according to the directions for use. The time of instillation will be recorded.

- *15-Minute Onset of Action CAC*: Each subject will receive one drop of the allergen solution bilaterally of the same allergen and dose that elicited a positive reaction at Visit 2, 15 minutes (+1 minute) post-instillation of investigational product.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1)

minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**).

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Slit Lamp Biomicroscopy*
- *Intraocular Pressure*
- *Dilated Fundoscopy*
- *Relief Drop Instillation:* Relief drop use should be recorded on the Concomitant medication log.
- *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 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 not limited to:

- Update of Medical/Medication History
- Assessment of Adverse Events
- Best Corrected VA at Distance Utilizing an ETDRS chart
- Slit Lamp Biomicroscopy
- IOP
- Dilated Fundoscopy

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)
- manifest clinically active signs or symptoms of allergic conjunctivitis during the ocular and nasal allergic signs and symptoms assessment at Visit 5
- sponsor termination of study
- other

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

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

8.6.3 Re-Screening:

If a subject screen failed due to inclusion/exclusion criteria and are now eligible, they may be rescreened. If a subject had COVID at the time of screening they may be rescreened after COVID symptoms have resolved.

Rescreening should occur at Visit 1 and subjects will be assigned a new screening number and sign a new consent.

8.7 Study Termination

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

8.8 Study Duration

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

8.9 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]

[redacted]

CRO 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 EOS 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 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 the first dose of the investigational drug (Visit 4a) and for 1 month after the last dose of investigational drug (Visit 5), 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 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 Visit 1.

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 Assessment of Efficacy

10.1.1 Primary Efficacy

The primary efficacy endpoints are:

- Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Conjunctival redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

Statistical success will be achieved if all of the following conditions are met at Visits 4b for duration of action and Visit 5 for onset of action:

- The Combo is superior in ocular itching and ocular redness to Vehicle.
- The Combo is superior in ocular itching to brimonidine tartrate 0.025%.
- The Combo is superior in ocular redness to ketotifen fumarate 0.035%.

Each primary endpoint will be summarized by post-CAC timepoint at each visit by treatment group using continuous summary statistics and analyzed using an ANCOVA model with terms for baseline value and treatment for the ITT population. Missing data will be imputed using multiple imputation methods. Least square means for each treatment

group and for the difference between treatment groups will be presented from the model together with two-sided p-values and 95% confidence intervals. Sensitivity analyses will also be performed by repeating the primary efficacy analysis on the PP population. Supportive analyses will be performed by comparing treatment groups using two-sample t-test and Wilcoxon rank sum tests. Superiority will be demonstrated for the first bullet point above if all of the following are true.

- For each endpoint, the estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and vehicle) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- For each endpoint, the estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- For each endpoint at each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided $\alpha = 0.0125=0.025/2$ to account for the two timepoints) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the timepoints, then the third time point is tested at the unused one-sided alpha of 0.0125.

Superiority will be demonstrated for the second and third bullet points above if all of the following are true.

- The estimated treatment effect (of the difference between ketotifen fumarate/brimonidine tartrate Combo ophthalmic solution and the comparator) is at least 0.5 units (one step) on a 5-point (nine step) scale at all three post-CAC time points at each of Visit 4b and 5.
- The estimated treatment effect is at least 1.0 unit (two steps) at two or three post-CAC time points at both Visits 4b and 5.
- At each visit, hypothesis testing will start with the first two post-CAC time points. If the treatment effect is statistically significant (one-sided $\alpha = 0.0125=0.025/2$ to account for the two timepoints) at both post-CAC time points, then this condition is met. If the treatment effect is statistically significant at only one of the timepoints, then the third time point is tested at the unused one-sided alpha of 0.0125.

10.1.2 Secondary Efficacy

The secondary endpoints are:

- Ciliary redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Episcleral redness score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5

Statistical inference for the secondary endpoints will only be performed if the primary efficacy analyses are considered successful. Secondary endpoints will be evaluated hierarchically in the order presented above. Success for each secondary endpoint will follow the same criteria as the primary endpoint. Sensitivity analyses for the secondary endpoints will be performed in the same manner as the sensitivity analyses for the primary endpoints.

10.1.3 Exploratory Efficacy Measures

Exploratory efficacy measures include:

- Eyelid swelling score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, not allowing half unit increments) at Visits 4b and 5
- Tearing score (average score of the subject's two eyes) evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5
- Chemosis score (average score of the subject's two eyes) evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b and 5
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, not allowing half unit increments) at Visits 4b and 5

The exploratory endpoints will be analyzed in the same manner as the primary efficacy endpoints. P-values for all exploratory results will be considered descriptive.

10.1.4 Statistical Hypothesis Testing and Control of Multiplicity

Superiority Tests

For each primary endpoint at each of the six evaluation times, (three evaluation times per visit), two superiority hypotheses will be tested comparing the Combo to a comparator (Vehicle and either ketotifen fumarate 0.035% or brimonidine tartrate 0.025%). The null hypothesis (H_0) is that the mean score for the subjects in the test (Combo) group (μ_T) is greater than or equal to the mean score for the subjects in the comparator group (μ_C). The alternative hypothesis (H_1) is that the mean score for the subjects in the test group is less than the mean score for the subjects in the comparator group.

$$H_0: \mu_T \geq \mu_C$$

$$H_1: \mu_T < \mu_C$$

The hypotheses above will be tested for each of the six post-instillation times at Visits 4b and 5 (three post-instillation times per visit). Success will be determined as per the criteria in Section 10.1.1.

Statistical inference will be performed for the secondary efficacy endpoints only if the primary efficacy endpoints demonstrate success and statistical inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order from the list of endpoints in Section 10.1.2.

10.1.5 General Considerations

Quantitative variables, including demographics at baseline, will be summarized descriptively using number of subjects (n), mean, median, standard deviation, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

Differences between treatment groups will be calculated as Combo minus Vehicle, Combo minus brimonidine tartrate 0.025%, or Combo minus ketotifen fumarate 0.035%.

Baseline values will be defined as the last non-missing measure prior to initiation of study treatment. Change from baseline will be calculated as follow-up measure minus baseline measure.

For efficacy and non-ocular safety analyses, the unit of analysis will be the subject. In the cases where assessments are recorded for each eye, the average of the eyes will be used. Adverse events will also be summarized at the subject level; if an AE occurs in either or both eyes, the subject will be counted as having the AE. For other ocular safety analyses, the unit of analysis will be each eye (with summaries showing results for the right eye (OD) and the left eye (OS) separately).

Statistical methods will be more fully described in a separate Statistical Analysis Plan.

10.1.6 Missing Efficacy Data Imputations

The primary efficacy analysis will be conducted with intercurrent events handled in the following manners:

1. Withdrawal due to lack of efficacy or adverse events [assumed to be missing not at random (MNAR)]: missing data will be imputed employing single imputation using worst observation carried forward [hypothetical strategy]
2. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events [assumed to be missing at random (MAR)]: missing data will be imputed employing multiple imputation using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology to impute non-monotone missing and using randomized treatment-based regression methodology to impute monotone missing [hypothetical strategy].

Intercurrent events for secondary efficacy analyses will be handled utilizing the same strategy for the primary efficacy analysis, with the following addition:

3. Discontinuation of study drug will be ignored (that is, measured values will be used regardless of compliance or discontinuation of study drug) [treatment policy strategy].

Additional sensitivity analyses will also be performed using observed data only.

10.1.7 Sensitivity Efficacy Analyses

Supportive analyses on the primary efficacy endpoint will include an evaluation of the treatment effect using two-sample t-tests and Wilcoxon rank sum tests.

The analysis on the primary efficacy endpoint will be repeated on the PP population with imputation and on the PP and FAS populations without imputation as sensitivity analyses.

Sensitivity analyses for secondary efficacy analyses will be performed in the same manner as the sensitivity analyses for the primary efficacy analyses.

Additional sensitivity analyses will be performed assuming all missing values due to withdrawal of any kind imputed employing:

- Single imputation using worst observation carried forward.
- Multiple imputation using randomized treatment-based regression methodology
- Control-based multiple imputation for subjects who drop out due to adverse events and/or lack of efficacy

10.1.8 Subgroup Analyses

Subgroup analyses will be performed on the primary and secondary efficacy endpoints by age group, sex, and race.

Any other planned subgroup analyses will be formally described in the study Statistical Analysis Plan.

10.2 Assessment of Safety

The following safety variables will be recorded:

- Adverse Events (AEs; reported, elicited and observed)
- VA at Distance Utilizing an ETDRS chart
- Slit Lamp Biomicroscopy
- IOP
- Dilated Fundoscopy

All safety parameters will be analyzed using the safety population. The safety of Combo compared to brimonidine tartrate 0.025%, ketotifen fumarate 0.035%, and vehicle will be assessed by the review of all of the safety parameters.

The results of the slit lamp biomicroscopy, IOP, and visual acuity will be presented by treatment at Baseline (Visit 4a) with numerical summaries. Change from baseline to Visits 4b, pre-CAC Visit 5, and Post-CAC Visit 5 will also be presented in the same manner. Shift tables will be presented to assess the results of the dilated fundoscopy. For assessments performed by eye, left eye and right eye will be summarized separately.

10.2.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events (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.

10.2.2 Safety Laboratory Tests

No safety laboratory tests will be conducted for this study.

10.2.3 Vital Sign Measurements

Vital signs will not be assessed.

10.2.4 Concomitant Medications

All previous concomitant medications will be classified based on terminology from the WHO Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

10.3 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study. Disposition will be summarized by treatment group and for all subjects.

The number of randomized subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment.

The number and percentage of subjects who prematurely discontinue from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects.

10.4 Demographics and Baseline Characteristics

Subject demographics including age, sex, ethnicity, race and baseline characteristics including results of ophthalmoscopy will be summarized using the appropriate descriptive statistics.

10.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations (including categorizations of major and minor) will be presented.

Important protocol deviations leading to exclusion from the Per-Protocol Population will include the following.

- Ineligibility
- Missing primary endpoint data at any time point of Visits 4b and 5
- Out of window primary endpoint data at any time point of Visits 4b and 5
- Use of any prohibited medication potentially affecting the primary endpoint at Visits 4b and 5

Additional important deviations leading to exclusion from the Per-Protocol Populations may be identified prior to unmasking of the treatment assignments.

10.6 Compliance

Compliance will not be evaluated in this study.

10.7 Interim Analyses

There are no interim analyses planned for this study.

10.8 Additional Statistical Considerations

10.8.1 Analysis Populations

- *Intent to Treat Set (ITT):* The ITT population will consist of all randomized subjects who are instilled with study drug. The ITT population will be analyzed as randomized.

- *Full Analysis Set (FAS):* The FAS will consist of all randomized subjects who are instilled with study drug and have at least one post-instillation of IP assessment of both primary endpoints. The FAS population will be analyzed as randomized.

- *Per Protocol Set (PP Set):* The PP Set will consist of FAS subjects with no protocol violations considered to affect the evaluability of efficacy, as determined through masked review of deviations prior to unmasking. The PP population will be analyzed as treated.

- *Safety Set:* The Safety Set will include all subjects who receive any amount of study medication. The safety population will be analyzed as treated.

10.8.2 Sample Size Determination

A sample size of 40 subjects in each treatment group will have at least 98% power to detect a difference in means of 1 unit at each time point assuming that the common standard deviation is 1 unit using a two-group t-test with a 1.25% one-sided significance level. Given that both efficacy measures (itching and redness) must pass to declare success, the overall power is at least 96%. To allow for 10% dropouts, 45 subjects will be randomized in each of the treatment groups.

10.8.3 Multicenter Issues

The study will be conducted at approximately 3 investigational centers in North America with the intention of pooling the results for analysis. Site specific data summaries for the primary endpoint, however, will be presented.

10.8.4 Multiplicity Issues

The Type I error rate for the primary efficacy analysis will be controlled by requiring the primary efficacy hypotheses test results to be statistically significant for all conditions in Section 10.1.1 to declare success for the primary endpoints. The overall Type I error rate including the primary and secondary efficacy analyses will be controlled by a hierarchical testing structure. Specifically, statistical inference for the secondary efficacy analyses will only be performed if the primary analyses are successful, after which inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order of the secondary endpoints from Section 1.1.2.

10.8.5 Windowing Rules

The timing of all study visits is relative to Baseline (Day 1).

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 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 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 EKGs. 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

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.

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

Not Applicable.

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

1. Abelson MB, Chapin MJ, Smith L. Ocular Allergic Disease: Mechanisms, Disease Subtypes, Treatment. *The Ocular Surface*, July 2003; 1(3):38-60.

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3. Ackerman SL, Torkildsen GL, McLaurin E, Vittitow JL. Low-dose brimonidine for relief of ocular redness: integrated analysis of four clinical trials. *Clin Exp Optom.* 2019;102(2):131-139.

4. Bielory L. Allergic and immunologic disorders of the eye. Part II: ocular allergy. J Allergy Clin Immunol 2000; 106:1019–1032.

5. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D and the ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol 2008; 19:110-124.

6. Hesselmar B, Aberg B, Eriksson B, Aberg N. Allergic rhinoconjunctivitis, eczema, and sensitization in two areas with differing climates. Pediatr Allergy Immunol 2001; 12:208–215.

7. Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. Curr Opin Allergy Clin Immunol 2011 Oct;11(5):471-6.

8. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010 Oct;126(4):778-783.e6.

9. Steering Committee (No authors listed). Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998; 351:1225 – 1232.

10. Alaway, Ketotifen Fumarate Ophthalmic Solution, 0.035%. Label approved April 2021

11. Lumify, Brimonidine Tartrate Ophthalmic Solution, 0.025%. Label approved September 2020

13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Visit	Visit 1	Visit 2	Visit 3	Visit 4a	Visit 4b	Visit 5
Day	-52 to -22	-21±3	-14±3	1	(8 hours from Visit 4a)	15±3
PROCEDURE						
General Assessments						
Informed Consent & HIPAA[1]	X					
Demographic Data	X					
Medical & Medication History	X					
Update Medical & Medication History		X	X	X	X	X
Allergic Skin Test	X					
Urine Pregnancy Test		X		X		X
Review Incl./Excl. criteria	X	X	X	X		
Enrollment/Randomization				X		
AE (TEAE[2]) Assessment	X	X	X	X	X	X
Allergen Challenge						
Titration CAC		X				
Confirmation CAC			X			
8 Hour Duration of Action CAC					X	
15 Minute Onset of Action CAC						X
Signs and Symptoms Assessments[3]		X	X	X	X	X
Relief Drop Instillation[4]		X	X		X	X
Visual/Systems Exams						
Visual Acuity Utilizing an ETDRS chart		X	X	X	X	X
Slit Lamp Biomicroscopy		X	X	X	X	X
Intraocular Pressure		X				X
Dilated Fundoscopy		X				X
Investigational Product						
IP Instillation				X[5]		X[6]
Drop Comfort & Descriptor Assessment				X		

[11] In the event that a subject has a medical condition, medication/contact lens washout, or needs to speak with the Investigator prior to Visit 1, the subject will be given an informed consent form. Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).
[2] Applicable to Visits 4a (post IP instillation), 4b, and 5 only.
[3] Performed pre-CAC and post-CAC. Note: pre/post CAC is not applicable for Visit 4a.
[4] Relief medication may be administered to subjects at the end of Visits 2, 3, 4b, and 5, after all evaluations have been completed. Relief drop use should be recorded on the Concomitant medication log.
[5] 8 hour (+1 hour) pre-CAC
[6] 15 (+1) minutes pre-CAC

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.

Slit Lamp Biomicroscopy Procedures

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). The following will be examined:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Eyelid

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

Dilated Fundoscopy

Dilated fundus exams will be performed using indirect ophthalmoscopy. The investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the investigator that may interfere with 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

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

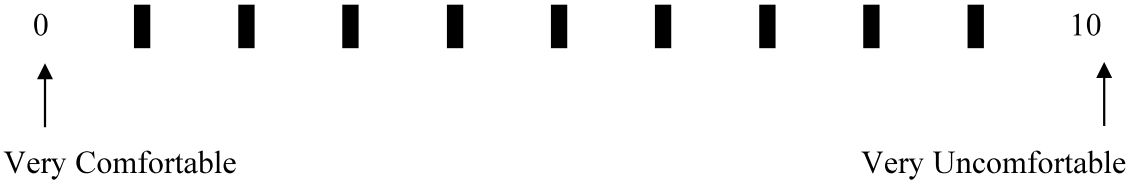
Drop Comfort Assessments

These procedures will be performed according to Ora, Inc. SOPs and/or guidance documents.

Subject-Reported Drop Comfort:

Drop comfort will be assessed for each eye immediately upon instillation, and at 1 (± 0.5 minutes) and 2 minutes (± 0.5 minutes) following initial dosing at Visit 4a using the Ora Calibra® Drop Comfort Scale:

Ora Calibra® Drop Comfort Scale



Subject-Reported Drop Comfort Questionnaire:

Description of drop comfort will be assessed at 3 minutes following initial dosing at Visit 4a using the Ora Calibra® Drop Comfort Questionnaire:

Ora Calibra® Drop Comfort Questionnaire

The subjects will be asked to choose 3 words that best describe how each eye drop feels in both of his/her eyes:

OTHER: _____

ALLERGEN CHALLENGE SCALES

Subject-Evaluated Symptoms (Ocular and Nasal)

Ocular Symptoms

Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale
Itching:

0 = None
0.5 =
1.0 =
1.5 =
2.0 =
2.5 =
3.0 =
3.5 =
4.0 =

0.5 unit increments ARE allowed

Ora Calibra™ Conjunctival Allergen Challenge Eyelid Swelling Scale
Eyelid Swelling:

0 = None
1.0 = Mild –
2.0 = Moderate –
3.0 = Severe –

0.5 unit increments are NOT allowed

Ora Calibra™ Conjunctival Allergen Challenge Tearing/Watery Eyes Scale
Tearing/Watery Eyes:

0 = None/Normal
1 = Mild –
2 = Moderate –
3 = Severe –
4 = Very Severe –

0.5 unit increments are NOT allowed

Ora proprietary scales – Not for distribution without permission

Nasal Allergic Symptoms

Ora Calibra™ Rhinorrhea Scale

Rhinorrhea (Runny Nose):

0= None
1= Mild [redacted]
2= Moderate [redacted]
3= Moderate/Severe [redacted]
4= Severe [redacted]

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Nasal Pruritus Scale

Nasal Pruritus (Itchy Nose):

0= None
1= Mild [redacted]
2= Moderate [redacted]
3= Moderate/Severe [redacted]
4= Severe [redacted]

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Ear or Palate Pruritus Scale

Ear or Palate Pruritus (Itchy Ear or Palate):

0= None
1= Mild [redacted]
2= Moderate [redacted]
3= Moderate/Severe [redacted]
4= Severe [redacted]

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Nasal Congestion Scale

Nasal Congestion:

0= None [redacted]
1= Mild [redacted]
2= Moderate [redacted]
3= Moderate/Severe [redacted]
4= Severe [redacted]

0.5 unit increments ARE NOT allowed.

Ora Proprietary Scales – Not for distribution without permission

Investigator-Evaluated Signs (Ocular)

Ora Calibra™ Ocular Hyperemia Scale

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

0 = None
1 = Mild – [redacted]
2 = Moderate – [redacted]
3 = Severe – [redacted]
4 = Extremely Severe – [redacted]

0.5 unit increments ARE allowed

Ora Calibra™ Chemosis Scale

Chemosis:

0 = None
1.0 = [redacted]
2.0 = [redacted]
3.0 = [redacted]
4.0 = [redacted]

0.5 unit increments ARE allowed

Ora Proprietary Scales – Nor for distribution without permission

APPENDIX 3: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

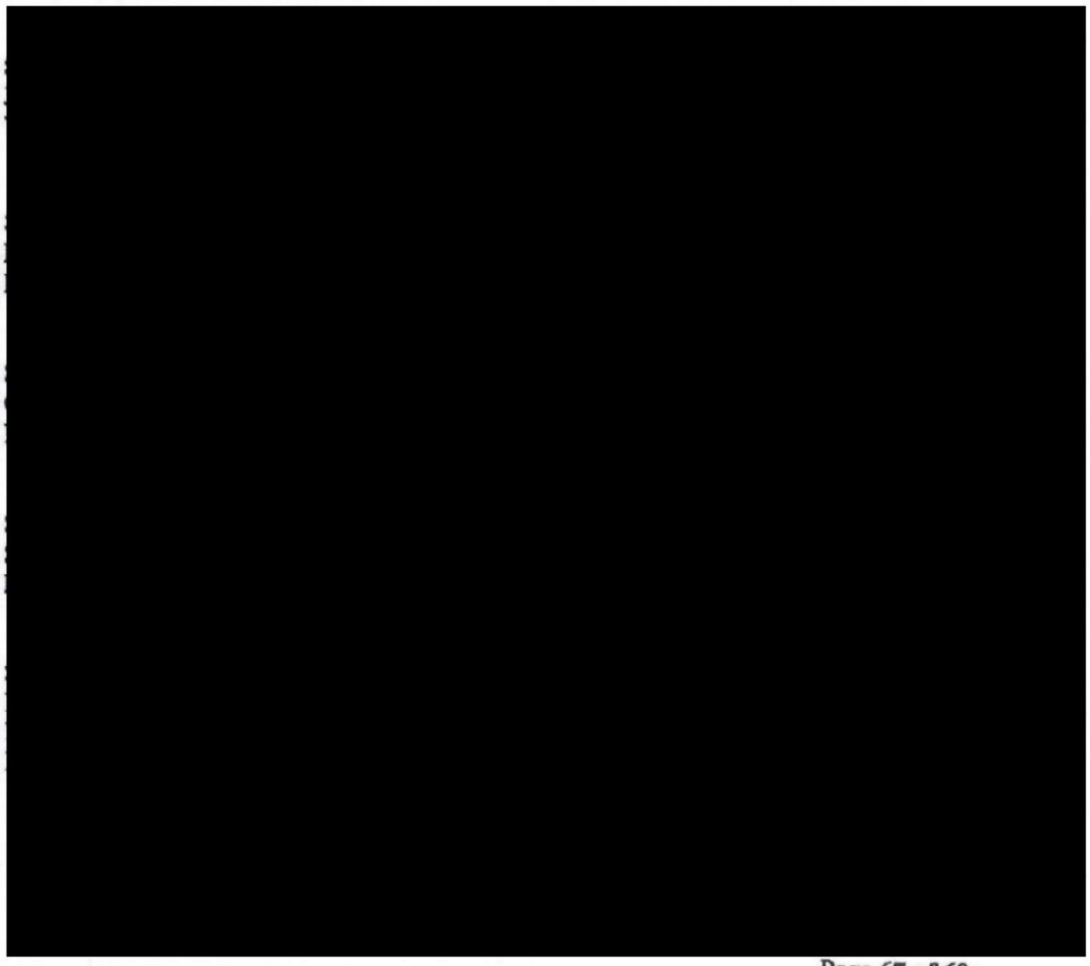
APPENDIX 4: PROTOCOL AMENDMENT SUMMARY

Please refer to Summary of Changes Document.

APPENDIX 5: SPONSOR APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025% /Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model
Protocol Number:	909
Final Date:	03Apr2023

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 6: ORA APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025% /Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model
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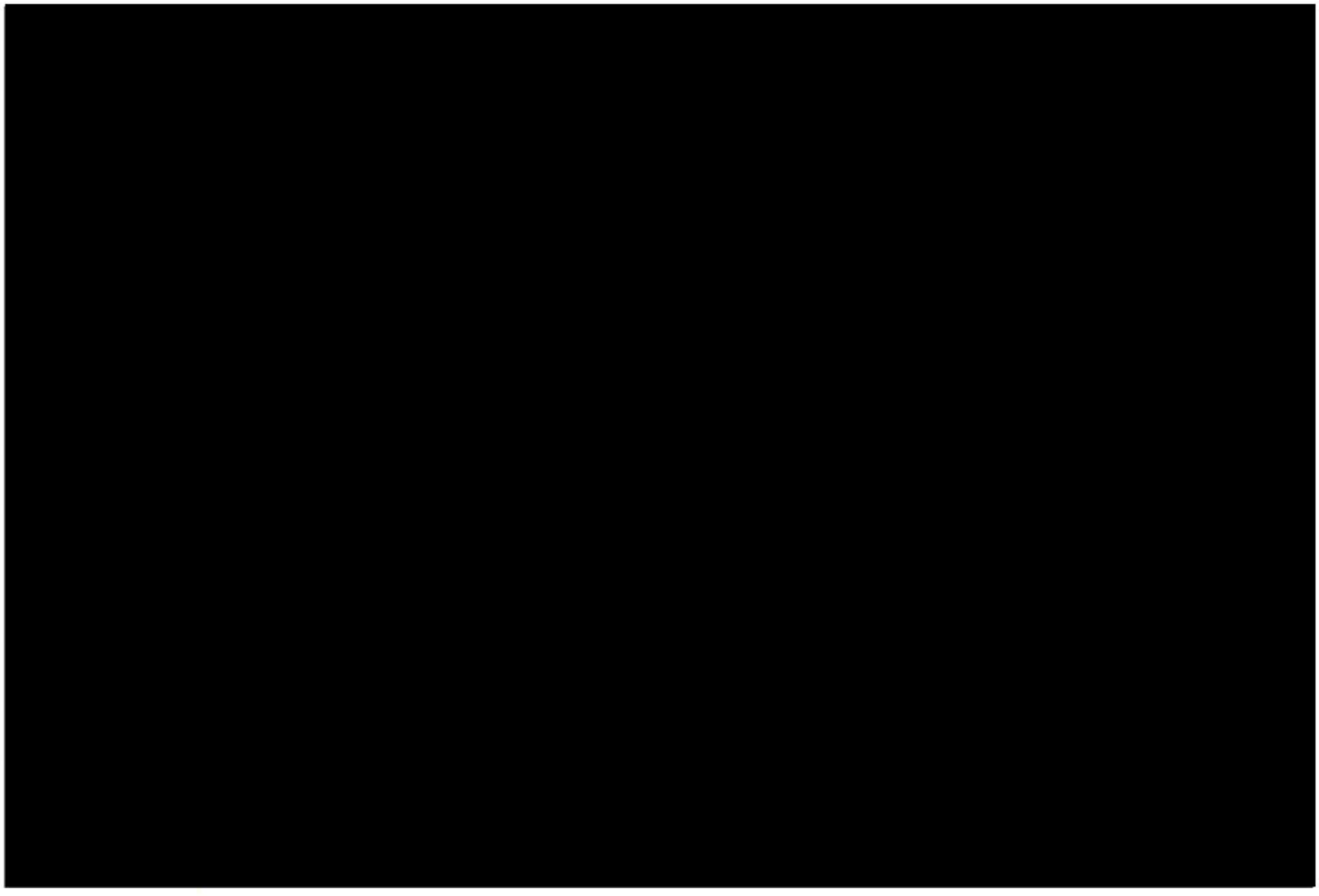

APPENDIX 7: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled Evaluation of the Onset and Duration of Action of the Combination Drug Product Brimonidine Tartrate 0.025%/Ketotifen Fumarate 0.035% Ophthalmic Solution Compared to its Components and Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge Model
Protocol Number:	909
Final Date:	03Apr2023

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>