Clinical Trial Protocol: 910

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 in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	910
Study Phase:	3
Investigational Product Name:	Brimonidine Tartrate 0.025%/ Ketotifen Fumarate 0.035% Ophthalmic Solution (Combo)
IND Number:	153035
Indication:	Seasonal Allergic Conjunctivitis
Investigators:	Multi-Center 8 sites
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:	30 June 2022
Amendment 1:	10 January 2023
Amendment 2:	31 Jul 2023

Confidentiality Statement

SPONSOR PERSONNEL

Sponsor:	Bausch & Lomb Incorporated 400 Somerset Corporate Boulevard Bridgewater, NJ 08807
Sponsor Representative (if different):	[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 in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	910
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 compared to vehicle in a population of subjects with seasonal allergic conjunctivitis.
Secondary Objective(s):	Not Applicable.
Overall Study Design:	
Structure:	The study will consist of 2 visits: a screening visit to verify subjects are eligible to participate and a qualification/treatment visit 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 90 minutes of exposure to pollen[1] in the ABC®. Subjects who have a sufficient ocular allergy score (defined as a

[1] Exposure will be to an allergen that elicited a positive reaction via skin testing.

	bilateral score of ≥2 in both ocular itching and ocular redness) at the 90 minute time point will be randomized 1:1:1:1 to receive one of the following bilaterally at Visit 2: • Brimonidine tartrate 0.025%/ Ketotifen Fumarate 0.035% combination ophthalmic solution (Combo) • Ketotifen fumarate ophthalmic solution, 0.035% • Brimonidine tartrate ophthalmic solution, 0.025% • Vehicle ophthalmic solution *Treatment Period:* Treatment will begin at Visit 2 following the 90 minute time point. Following instillation of investigational product, randomized subjects will remain exposed to pollen in the ABC® for an additional 8 hours. Assessments will be conducted at the designated time points. If subjects do not have a sufficient ocular allergy score at the 90 minute time point and also have a positive skin test reaction to both ragweed and timothy grass, they may be re-screened for Visit 2 using the alternate pollen. In the event that subjects do not receive a full 90 minutes of pollen exposure (e.g. early exit from BioCube, mechanical issue with pollen distribution, etc.), subjects may also be eligible for re-screening. Re-screening should take place at least one week following the initial Visit 2 and should be within the specified study visit windows.
Duration:	This trial consists of 2 office visits over a period of approximately 2 to 61 days.
Controls:	• Ketotifen fumarate ophthalmic solution, 0.035% • Brimonidine tartrate ophthalmic solution, 0.025%

	• Vehicle ophthalmic solution
Dosage/ Instillation:	At Visit 2, a trained study technician will instill 1 drop of the assigned investigational product into each eye.
Summary of Visit Schedule:	Visit 1 (Day -60 to Day -1): Screening / Informed Consent / Skin Test Visit 2 (Day 1): ABC® Qualification Exposure/ Randomization/ Treatment / ABC® 8hr Exposure/ Exit
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 360 subjects will be screened in order to enroll approximately 224 subjects, 56 subjects per treatment group
Condition/Disease:	Seasonal Allergic Conjunctivitis.
Inclusion Criteria:	Subjects must: 1. be at least 18 years of age of either sex and any race; 2. provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. be willing and able to follow all instructions and attend all study visits; 4. provide proof of COVID-19 vaccination[2];

[2] Visit 2 should occur at least two weeks after full vaccination.

	5. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and for the duration of the visit; 6. have seasonal allergic conjunctivitis to ragweed or timothy grass documented by a self-reported history of ocular allergic symptoms for the last 2 consecutive years during the ragweed or timothy grass seasons and a positive skin test reaction to ragweed or timothy grass pollen as confirmed by the allergic skin test given at or within 24 months of the subject's Visit 1; 7. (If female and of childbearing potential) agree to have urine pregnancy testing performed at Visit 2 (must be negative); 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 and 1 month after receiving investigational drug. 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 receiving investigational drug (Visit 2). 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); 8. (If male and with female partner of childbearing potential) must use at least

	1 medically acceptable form of birth control. Note: Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to receiving investigational drug (Visit 2). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository throughout the study duration, for at least 14 days prior to and 1 month after investigational drug (Visit 2); 9. have a calculated visual acuity (VA) of 0.7 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Visit 1; 10. have a positive Allergen BioCube challenge response to pollen exposure at the 90 minute time point of ABC® exposure at Visit 2, defined as bilateral score of ≥2 in ocular itching and ocular redness.
Exclusion Criteria:	Subjects may not: 1. have known contraindications or sensitivities to the use of any of the investigational product medication or components; 2. have a history of mild persistent, moderate or severe asthma within the preceding 5 years according to the National Heart, Blood, and Lung Institute classification (with the exception of exercise induced asthma). **Note**: Subjects with fall induced asthma that is either mild persistent (defined as >1 per week, but <1 per day), moderate persistent, or severe persistent will be excluded. 3. have an upper respiratory tract or sinus infection within the previous 2 weeks of Visit 1;

	4. have a history of anaphylaxis or poor tolerability of previously administered allergen; 5. have a compromised lung function at Visit 1 (defined as a peak expiratory flow rate [PEFR] that is below 80% of the predicted average PEFR, as calculated by gender, age, and measured height from the Mini-Wright instruction's table: Normal Adult Predicted Average Peak Expiratory Flow). 6. have an abnormal blood pressure (defined as ≤ 90 or ≥ 160 (systolic) measured in mmHg or ≤ 60 or ≥ 100 (diastolic) measured in mmHg) at Visit 1; 7. 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); 8. have had ocular surgical intervention within three months prior to Visit 1, or during the trial or a history of refractive surgery six months prior to Visit 1, or have systemic surgery planned during the clinical trial or within 30 days after; 9. have a known history of retinal detachment, diabetic retinopathy, or active retinal disease; 10. have an active ocular infection (bacterial, viral or fungal), active uveitis, or positive history of an ocular herpetic infection at any visit; 11. use any of the following disallowed medications during the period indicated below **prior to Visit 2**: **3 Days** • systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer

	drug combinations, H1 antihistamine- vasoconstrictor drug combinations; **7 Days** • decongestants; • monoamine oxidase inhibitors; • all other topical ophthalmic preparations (including artificial tears); • lid scrubs; • prostaglandins or prostaglandin derivatives; • ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs); **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 2 and will continue to be maintained for the duration of the trial.* **14 Days** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **45 Days** • depot-corticosteroids; **60 Days** • immunosuppressive or cancer chemotherapeutic agents; 12. have any significant illness (including, but not limited to, poorly controlled hypertension, poorly controlled diabetes, a history of status asthmaticus, a history of organ transplantation, a history of persistent moderate or severe asthma, a history of moderate to severe allergic asthmatic reactions to any of the clinical trial allergens, any autoimmune disease requiring therapy, or severe cardiovascular disease or arrhythmia) that, at the investigators' discretion, could be expected to interfere with the subject's health or with the clinical trial

	parameters or put the subject at any unnecessary risk; 13. have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg in either eye at Visit 1; 14. develop a compromised lung function (defined as a PEFR drop of 15% or more from Visit 1 baseline value) at Visit 2[3]; 15. have used an investigational drug or medical device within 30 days of Visit 1 or be concurrently enrolled in another investigational trial; 16. be a female who is currently pregnant, planning a pregnancy, or lactating; 17. have symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19; 18. have been randomized in the Bausch & Lomb 909 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.

[3] If occurs at more than one assessment, per the investigator's discretion.

	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 Effectiveness Parameters** • Ocular itching score (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Ocular redness (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] **Secondary Effectiveness Parameters** • Tearing evaluated by the subject (average score of the subject's two eyes) at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Lid swelling (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Chemosis (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1),

	30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
Exploratory Measures:	• Nasal itching evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted], NOT allowing half unit increments) • Rhinorrhea evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Nasal congestion evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Sneezing evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted] • Total nasal symptom scores (TNSS) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (composite score of Nasal Itching, Nasal Congestion, Rhinorrhea and Sneezing) • Peak Nasal Inspiratory Flow (PNIF) measured pre-ABC® exposure to 8 hours post-instillation of assigned IP at Visit 2 (measured by means of a peak flow meter in L/min)
Safety Measures:	• Adverse Events (AEs; reported, elicited and observed) • Best Corrected VA at Distance Utilizing an ETDRS chart

	• Slit Lamp Biomicroscopy • Intraocular Pressure (IOP) • Dilated Fundoscopy • Vital signs • Peak Expiratory Flow Rate (PEFR)

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.

Unit of Analysis

The primary efficacy parameters are measured at the subject level and will be summarized as such.

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, vital signs, and peak expiratory flow rate will be summarized descriptively.

Primary Effectiveness Analyses

Statistical success will be achieved if all of the following conditions are met at Visit 2.

1. The Combo is superior in ocular itching to Vehicle.
2. The Combo is superior in ocular redness to Vehicle.

3. The Combo is superior in ocular itching to brimonidine tartrate ophthalmic solution, 0.025%.
4. The Combo is superior in ocular redness to ketotifen fumarate ophthalmic solution, 0.035%.

Superiority will be demonstrated for comparisons above if the treatment effect is statistically significant in accordance with the below.

Hypothesis testing will be split into two groups. Hypotheses associated with the first three time points will constitute the first group and hypotheses associated with the latter three time points will constitute the second group.

Testing of the first three time points will be performed first. If the treatment effect is not statistically significant (one-sided $\alpha = 0.0083=0.025/3$ to account for the three timepoints) at any of the three time points, then the condition is not met.

If the treatment effect is statistically significant for at least one of the first three timepoints, then the second group of hypotheses is tested.

If the treatment effect was statistically significant for exactly one of the three comparisons in the first group, this leaves 0.0083 alpha unused and all three treatment effects in the second group of hypotheses must be statistically significant at the unused one-sided alpha=0.0083/3=0.0028 in order for this condition to be met.

If the treatment effect was statistically significant for exactly two of the three comparisons in the first group, this leaves 0.0167 alpha unused and at least two treatment effects in the second group of hypotheses must be statistically significant at the unused one-sided alpha=0.01673=0.0056 in order for this condition to be met.

If the treatment effect was statistically significant for all three comparisons in the first group, this leaves 0.025 alpha unused, and at least one treatment effect in the second group of hypotheses must be statistically significant at the unused one-sided alpha=0.025/3=0.0083 in order for this condition to be met.

Hypotheses

For each primary endpoint (ocular itching and ocular redness) at each of the six evaluation time points post-instillation of IP, superiority hypotheses will be tested comparing the Combo to a comparator ketotifen fumarate 0.035% (for ocular redness), brimonidine tartrate 0.025% (for ocular itching), or Vehicle (for ocular redness and ocular itching)]. The null hypothesis (H_0) is that the mean score for the subjects in the 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 control group.

$$H_0: \mu_T \geq \mu_C$$
$$H_1: \mu_T < \mu_C$$

Methods

Each primary endpoint will be summarized by post-instillation of IP time point at Visit 2 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..

Secondary summaries of the primary endpoints by post-instillation of IP time point at Visit 2 will be given for the difference in mean ocular itching between the Combo and ketotifen fumarate 0.035% and between ketotifen fumarate 0.035% and vehicle as well as for the difference in mean ocular redness between the Combo and brimonidine tartrate 0.025% and between brimonidine tartrate 0.025% and vehicle. Missing data will be imputed using multiple imputation techniques. Continuous summary statistics including two-sided 95% t-distribution confidence intervals around the difference in means will be provided.

Sample Size Calculations:

A sample size of 50 subjects in each treatment group yields 95% power to demonstrate each of the following:

- Combo is superior to vehicle in ocular itching (evaluated by the subject)
- Combo is superior to vehicle in ocular redness (evaluated by the Investigator)
- Combo is superior to brimonidine tartrate ophthalmic solution, 0.025% in ocular itching (evaluated by the subject)
- Combo is superior to ketotifen fumarate ophthalmic solution, 0.035% in ocular redness (evaluated by the Investigator)

assuming a one-sided $\alpha = 0.0028$, a true mean difference of 0.65 units and a common standard deviation of 1.0 units at each time point for each measure.

To allow for 10% dropouts, 56 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).

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABC®	Allergen BioCube®
AE	adverse event
BAK	benzalkonium chloride
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRO	contract research organization
DHHS	Department of Health and Human Services
ECG	electrocardiogram
eCRF	electronic case report form
EEU	environmental exposure unit
EOS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical 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
logMAR	logarithm of the minimum angle of resolution
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
NCS	not clinically significant
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OTC	over the counter
PEFR	peak expiratory flow rate

PNIF	peak nasal inspiratory flow
PP	per protocol
RTSM	Randomization and Trial Supply Management
SAC	seasonal allergic conjunctivitis
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TNSS	total nasal symptom score
USP	United States Pharmacopeia
VA	visual acuity

1 INTRODUCTION

Allergic conjunctivitis is a common yet underdiagnosed inflammatory condition of the eye that affects the quality of life of patients worldwide (Rosario, 2011; Leonardi, 2015; Dupuis, 2020; Alexander, 2005). The prevalence of allergic conjunctivitis has been on the rise over the past several decades and it is estimated that up to 40% of the North American population is affected (Singh, 2010; Brozek, 2015).

Acute allergic conjunctivitis represents the majority of all ocular allergy incidences and 95% can be classified as intermittent/seasonal or persistent/perennial, depending on the frequency of symptoms throughout the year which is dictated by the type of environmental allergens (O'Brien, 2013; Butrus, 2005; Bielory, 2019). Intermittent or seasonal allergic conjunctivitis, also known as hay fever, is caused by outdoor allergens, such as tree or grass pollen, and is usually experienced during the warmer months. Persistent or perennial allergic conjunctivitis is caused by indoor allergens, like dust mites or animal dander, and is experienced year-round. Both types of acute allergic conjunctivitis present bilaterally and are characterized by the hallmark ocular symptom of pruritus (itching) and sign of redness (Ono, 2005; Palmares, 2010; Villegas, 2021; Bielory, 2012). Patients may also experience tearing, discharge, or swelling, and often suffer from other comorbidities such as allergic rhinitis and asthma (Rosario, 2011; Miyazaki, 2020).

Acute allergic conjunctivitis occurs in previously sensitized individuals when environmental allergens contact the ocular mucosa and trigger a type 1 allergic response (Dupuis, 2020). This type 1 response is defined by IgE-mediated mast cell degranulation and can be divided into an early phase and a late phase. The early phase occurs within seconds and lasts up to 30 minutes during which mast cells release preformed mediators (e.g., histamine, tryptase) followed by the synthesis and release of additional mediators and cytokines (e.g., leukotrienes, prostaglandins, IL-4). The late phase occurs after several hours and is characterized by the recruitment and infiltration of active inflammatory cells that continue to cause inflammation which can lead to tissue damage (Ono, 2005; Chigbu, 2018).

The Allergen BioCube® (ABC®) is an environmental exposure unit (EEU) that allows for precise control over the type and concentration of allergen to which a patient is exposed. Additionally, confounding factors such as temperature and air quality can be regulated to reduce variability within and between studies. The ABC® has been technically and clinically validated for both timothy grass and ragweed pollen in allergic conjunctivitis and allergic rhinitis. In these studies, the ABC® uniformly distributed these allergens at prespecified concentrations which reproduced clinically relevant signs and symptoms upon patient exposure (Gomes, 2016; Angjeli, 2017). The ABC® has also been used to assess the efficacy of both known (fluticasone furoate nasal spray) and unknown (iodixanol) drugs in the treatment of allergic rhinitis (Lane, 2011; Gomes, 2019).

Current therapies for allergic conjunctivitis 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 seasonal 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, 2003; Alaway® Ketotifen Fumarate Ophthalmic Solution, 0.035% (OTC) Label, approved accessed 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 2020 accessed). 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 compared to vehicle in a population of subjects with seasonal allergic conjunctivitis.

3 CLINICAL HYPOTHESES

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

4 OVERALL STUDY DESIGN

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

The study will consist of 2 visits: a screening visit to verify subjects are eligible to participate and a qualification/treatment visit 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 90 minutes of exposure to pollen[4] in the ABC®. Subjects who have a sufficient ocular allergy score (defined as a

[4] Exposure will be to an allergen that elicited a positive reaction via skin testing.

bilateral score of ≥2 in both ocular itching and ocular redness) at the 90 minute time point will be randomized 1:1:1:1 to receive one of the following bilaterally at Visit 2:

- Brimonidine tartrate 0.025%/ Ketotifen fumarate 0.035% combination ophthalmic solution (Combo)
- Ketotifen fumarate ophthalmic solution, 0.035%
- Brimonidine tartrate ophthalmic solution, 0.025%
- Vehicle ophthalmic solution

Treatment will begin at Visit 2 following the 90 minute time point. Following instillation of investigational product, randomized subjects will remain exposed to pollen in the ABC® for an additional 8 hours. Assessments will be conducted at the designated time points.

If subjects do not have a sufficient ocular allergy score at the 90 minute time point and also have a positive skin test reaction to both ragweed and timothy grass, they may be re-screened for Visit 2 using the alternate pollen. In the event that subjects do not receive a full 90 minutes of pollen exposure (e.g. early exit from BioCube, mechanical issue with pollen distribution, etc.), subjects may also be eligible for re-screening. Re-screening should take place at least one week following the initial Visit 2 and should be within the specified study visit windows.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 360 subjects will be screened in order to enroll approximately 224 subjects, 56 subjects per treatment group.

5.2 Study Population Characteristics

Subjects of at least 18 years of age of either sex and any race, with a diagnosis of seasonal 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 18 years of age of either sex and any race;
2. provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;
3. be willing and able to follow all instructions and attend all study visits;

4. provide proof of COVID-19 vaccination[5];
5. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and for the duration of the visit;
6. have seasonal allergic conjunctivitis to ragweed or timothy grass documented by a self-reported history of ocular allergic symptoms for the last 2 consecutive years during the ragweed or timothy grass seasons and a positive skin test reaction to ragweed or timothy grass pollen as confirmed by the allergic skin test given at or within 24 months of the subject's Visit 1;
7. (If female and of childbearing potential) agree to have urine pregnancy testing performed at Visit 2 (must be negative); 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 and 1 month after receiving investigational drug. 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 receiving investigational drug (Visit 2). 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);
8. (If male and with female partner of childbearing potential) must use at least 1 medically acceptable form of birth control. Note: Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to receiving investigational drug (Visit 2). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository throughout the study duration, for at least 14 days prior to and 1 month after investigational drug (Visit 2);
9. have a calculated visual acuity (VA) of 0.7 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Visit 1;
10. have a positive Allergen BioCube challenge response to pollen exposure at the 90 minute time point of ABC® exposure at Visit 2, defined as bilateral score of $\geq$2 in ocular itching and ocular redness.

5.4 Exclusion Criteria

Exclusion Criteria:

Subjects may not:

1. have known contraindications or sensitivities to the use of any of the investigational product medication or components;

[5] Visit 2 should occur at least two weeks after full vaccination.

2. have a history of mild persistent, moderate or severe asthma within the preceding 5 years according to the National Heart, Blood, and Lung Institute classification (with the exception of exercise induced asthma).
   Note: Subjects with fall induced asthma that is either mild persistent (defined as >1 per week, but <1 per day), moderate persistent, or severe persistent will be excluded.
3. have an upper respiratory tract or sinus infection within the previous 2 weeks of Visit 1;
4. have a history of anaphylaxis or poor tolerability of previously administered allergen;
5. have a compromised lung function at Visit 1 (defined as a peak expiratory flow rate [PEFR] that is below 80% of the predicted average PEFR, as calculated by gender, age, and measured height from the Mini-Wright instruction's table: Normal Adult Predicted Average Peak Expiratory Flow).
6. have an abnormal blood pressure (defined as ≤ 90 or ≥ 160 (systolic) measured in mmHg or ≤ 60 or ≥ 100 (diastolic) measured in mmHg) at Visit 1;
7. 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);
8. have had ocular surgical intervention within three months prior to Visit 1, or during the trial or a history of refractive surgery six months prior to Visit 1, or have systemic surgery planned during the clinical trial or within 30 days after;
9. have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
10. have an active ocular infection (bacterial, viral or fungal), active uveitis, or positive history of an ocular herpetic infection at any visit;
11. use any of the following disallowed medications during the period indicated below **prior to Visit 2**:

    3 Days
    - systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer drug combinations, H1 antihistamine- vasoconstrictor drug combinations;

    7 Days
    - decongestants;
    - monoamine oxidase inhibitors;
    - all other topical ophthalmic preparations (including artificial tears);
    - lid scrubs;
    - prostaglandins or prostaglandin derivatives;
    - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

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

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

    45 Days

- depot-corticosteroids;

60 Days

- immunosuppressive or cancer chemotherapeutic agents;

12. have any significant illness (including, but not limited to, poorly controlled hypertension, poorly controlled diabetes, a history of status asthmaticus, a history of organ transplantation, a history of persistent moderate or severe asthma, a history of moderate to severe allergic asthmatic reactions to any of the clinical trial allergens, any autoimmune disease requiring therapy, or severe cardiovascular disease or arrhythmia) that, at the investigators' discretion, could be expected to interfere with the subject's health or with the clinical trial parameters or put the subject at any unnecessary risk;
13. have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) that is less than 5 mmHg or greater than 22 mmHg in either eye at Visit 1;
14. develop a compromised lung function (defined as a PEFR drop of 15% or more from Visit 1 baseline value) at Visit 2[6];
15. have used an investigational drug or medical device within 30 days of Visit 1 or be concurrently enrolled in another investigational trial;
16. be a female who is currently pregnant, planning a pregnancy, or lactating;
17. have symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19;
18. have been randomized in the Bausch & Lomb 909 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 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Ocular redness (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

[6] If occurs at more than one assessment, per the investigator's discretion.

6.1.2 Secondary Efficacy Measure(s) and Endpoints

- Tearing evaluated by the subject (average score of the subject's two eyes) at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Lid swelling (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 ([redacted]
- Chemosis (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

6.2 Exploratory Measures

- Nasal itching evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Rhinorrhea evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Nasal congestion evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Sneezing evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Total nasal symptom scores (TNSS) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (composite score of Nasal Itching, Nasal Congestion, Rhinorrhea and Sneezing)
- Peak Nasal Inspiratory Flow (PNIF) measured pre-ABC® exposure to 8 hours post-instillation of assigned IP at Visit 2 (measured by means of a peak flow meter in L/min)

6.3 Safety Measures

- Adverse Events (AEs; reported, elicited and observed)
- Best Corrected VA at Distance Utilizing an ETDRS chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Vital signs
- Peak Expiratory Flow Rate (PEFR)

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 = 56)
- Ketotifen fumarate ophthalmic solution 0.035% (n = 56)
- Brimonidine tartrate ophthalmic solution 0.025% (n = 56)
- Vehicle ophthalmic solution (n = 56)

7.1.2 Instructions for Use and Administration

- At Visit 2, a trained study technician will instill 1 drop of the assigned investigational product into each eye while subjects are in the ABC®.

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 in the ABC® (Ragweed and Timothy grass)

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 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:

3 Days
- contact lenses *(72 hour washout)*
- systemic or ocular H1 antihistamine, H1 antihistamine/mast-cell stabilizer drug combinations, H1 antihistamine- vasoconstrictor drug combinations;

7 Days
- decongestants;
- monoamine oxidase inhibitors;
- all other topical ophthalmic preparations (including artificial tears);
- lid scrubs;
- prostaglandins or prostaglandin derivatives;
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

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

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

45 Days
- depot-corticosteroids;

60 Days
- immunosuppressive or cancer chemotherapeutic agents;

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 2, 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
- monoamine oxidase inhibitors
- all other topical ophthalmic preparations (including artificial tears)
- lid scrubs
- prostaglandins or prostaglandin derivatives
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs)
  **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 2 and will continue to be maintained for the duration of the trial.*
- 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.

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 -60 to Day -1): Screening/ Informed Consent/ Skin Test

Informed Consent/HIPAA: Prior to any changes in a subject's medical treatment and/or any 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 thirty days (30), which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within the sixty days (60) 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.

- *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 exam will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality which are not exclusionary should be recorded as Medical History, as applicable.

- *Peak Expiratory Flow Rate (PEFR) Measurement*: Baseline PEFR measurement will be done (as outlined in Appendix 2) to exclude subjects with a compromised lung function (defined as a PEFR that is below 80% the predicted average).

- *Vital Signs*: Resting blood pressure and pulse will be measured. Subjects with an abnormal blood pressure (defined as ≤ 90 or ≥ 160 (systolic) measured in mmHg or ≤ 60 or ≥ 100 (diastolic) measured in mmHg) will be excluded.

- *Intraocular Pressure:* Intraocular pressure (IOP) will be measured in each eye by contact tonometry. Subjects with an IOP of less than 5 mmHg or greater than 22 mmHg in either eye 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.
- *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 for Visit 2.

8.3.1.1 VISIT 2 (Day 1): ABC Qualification Exposure/ Randomization/ Treatment/ ABC® 8hr Exposure/ Exit

- *Update of Medical/Medication History*: Collect and record any changes or new medications/conditions that may have started or that require follow-up from the last visit.

- *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.

- *Pre-ABC® 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 1 will be considered an adverse event.

- *Pre-ABC® Slit Lamp Biomicroscopy*

- *Pre-ABC® Ocular and Nasal Allergic Signs and Symptoms Assessment*

- *Peak Expiratory Flow Rate (PEFR) Measurement*: Subjects who develop a compromised lung function (defined as a PEFR drop of 15% or more from Visit 1

baseline value) may be excluded if occurs at more than one assessment, per the investigator's discretion.

- *Peak Nasal Inspiratory Flow*

- *Vital signs*

- *Review of Inclusion/Exclusion Criteria*

- *90 Minute Qualification Exposure in ABC®:* The study subjects will be exposed to ragweed or timothy grass pollen in the ABC® for 90 minutes prior to enrollment qualification review. Assessment of ocular and nasal allergic signs and symptoms will be evaluated by the subjects and Investigator at 90(±5) minutes during ABC® exposure. PEFR will be collected at 60(±15) minutes during exposure in the ABC®. PEFR measurement will be done to exclude subjects with a compromised lung function (defined as a PEFR drop of 15% or more from Visit 1 baseline value)[7]. Measurement of PNIF will be collected at 90(±15) minutes during exposure in the ABC®.

- *Review of Applicable Inclusion/Exclusion Criteria:* Subjects must have a bilateral score of ≥2 in ocular itching and ocular redness at the 90-minute timepoint.

  If subjects do not have a sufficient ocular allergy score at the 90 minute time point and also have a positive skin test reaction to both ragweed and timothy grass, they may be re-screened for Visit 2 using the alternate pollen. In the event that subjects do not receive a full 90 minutes of pollen exposure (e.g. early exit from BioCube, mechanical issue with pollen distribution, etc.), subjects may also be eligible for re-screening. Re-screening should take place at least one week following the initial Visit 2 and should be within the specified study visit windows.
- *Enrollment/Randomization*: Treatment will be randomly assigned in a 1:1:1:1 ratio according to the randomization schedule. 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. Randomization numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted.

- *Instillation of Investigational Product:* The assigned investigational product will be administered by a trained study technician. The technician will instill one drop of the assigned investigational product into each eye and the time of instillation will be recorded.

[7] If occurs at more than one assessment, per the investigator's discretion.

- *8 Hour Post-Treatment Exposure in ABC®:* Following instillation of investigational product, randomized subjects will be exposed to pollen in the ABC® for up to an additional 8 hours. Assessment of ocular and nasal allergic signs and symptoms will be evaluated by the subjects and Investigator at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of investigational product. Measurements of PNIF will be collected 60(±15) and 480(±15) minutes post-treatment. PEFR will be collected 120(±15), 240(±15), 360(±15), and 480(±15) minutes post-treatment.

  Subjects can exit the ABC® up to three times, for no longer than 15 minutes on each occasion, before it will be considered a protocol violation. Time of exit and re-entry will be recorded.

- *Post-ABC® Visual Acuity Utilizing an ETDRS Chart*
- *Post-ABC® Slit Lamp Biomicroscopy*
- *Intraocular Pressure*
- *Dilated Fundoscopy*
- *Adverse Event Query*
- *Study Exit*

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:

- Update of Medical/Medication History
- Assessment of Adverse Events
- Best Corrected VA at Distance Utilizing an ETDRS chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Peak Expiratory Flow Rate (PEFR)

8.5 Compliance with Protocol

At Visit 2, subjects are expected to remain exposed in the ABC® with the exception of any assessments that may need to be performed outside of the room. When necessary, subjects are allowed to exit the ABC® up to three times, for no longer than 15 minutes on each occasion, before it will be considered a protocol violation. Time of exit and re-entry will be recorded.

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)
- 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.

8.7 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 2 office visits over a period of approximately 2 to 61 days.

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.

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 Ora designee:

  CRO Contact:
  [redacted]

Once the SAE Report has been reviewed by the Medical Monitor, the form will be faxed or emailed to the following Sponsor designee:

Sponsor 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 eCRF 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, 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 and 1 month after receiving the investigational drug (Visit 2), 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/SAEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Final outcomes should be reported to Ora and Sponsor for post-study follow-up. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora Inc. within 24 hours. The original SAE form is

not to be altered. The report should describe whether the event has resolved or continues and how the event was treated

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 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

- Ocular redness (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

Statistical success will be achieved if all of the following conditions are met at Visit 2.

1. The Combo is superior in ocular itching to Vehicle.
2. The Combo is superior in ocular redness to Vehicle.
3. The Combo is superior in ocular itching to brimonidine tartrate 0.025%.
4. The Combo is superior in ocular redness to ketotifen fumarate 0.035%.

Each primary endpoint will be summarized by post-instillation of IP time point at Visit 2 by treatment group using continuous summary statistics for the FAS population, and sensitivity analyses will be performed on the PP population. Missing data will be imputed using multiple imputation techniques. Treatment effects will be estimated, and the statistical hypotheses will be tested using two-sample t-tests assuming equal variances.

Superiority will be demonstrated for comparisons above if the treatment effect is statistically significant in accordance with the below.

Hypothesis testing will be split into two groups. Hypotheses associated with the first three time points will constitute the first group and hypotheses associated with the latter three time points will constitute the second group.

Testing of the first three time points will be performed first. If the treatment effect is not statistically significant (one-sided $\alpha = 0.0083=0.025/3$ to account for the three timepoints) at any of the three time points, then the condition is not met.

If the treatment effect is statistically significant for at least one of the first three timepoints, then the second group of hypotheses is tested.

If the treatment effect was statistically significant for exactly one of the three comparisons in the first group, this leaves 0.0083 alpha unused and all three treatment effects in the second group of hypotheses must be statistically significant at the unused one-sided alpha=0.0083/3=0.0028 in order for this condition to be met.

If the treatment effect was statistically significant for exactly two of the three comparisons in the first group, this leaves 0.0167 alpha unused and at least two treatment effects in the second group of hypotheses must be statistically significant at the adjusted unused one-sided alpha=0.0167/3=0.0056 in order for this condition to be met.

If the treatment effect was statistically significant for all three comparisons in the first group, this leaves 0.025 alpha unused, and at least one treatment effect in the second group of hypotheses must be statistically significant at the adjusted unused one-sided alpha=0.025/3=0.0083 in order for this condition to be met.

Summaries of the primary endpoints by post-instillation of IOP time point at Visit 2 will be given for the difference in mean ocular itching between the Combo and ketotifen fumarate 0.035% and between ketotifen fumarate 0.035% and vehicle as well as for the difference in mean ocular redness between the Combo and brimonidine tartrate 0.025% and between brimonidine tartrate 0.025% and vehicle. Missing data will be imputed using multiple imputation techniques. Continuous summary statistics including two-sided 95% t-distribution confidence intervals around the difference in means will be provided

10.1.2 Secondary Efficacy

The secondary endpoints are:

- Tearing (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Lid swelling (average score of the subject's two eyes) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Chemosis (average score of the subject's two eyes) evaluated by the Investigator using slit lamp at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]

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 Endpoints

Exploratory endpoints include:

- Nasal itching evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (0-4 scale)
- Rhinorrhea evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Nasal congestion evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Sneezing evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 [redacted]
- Total nasal symptom scores (TNSS) evaluated by the subject at 10(±1), 30(±1), 60(±5), 360(±5), 420(±5), and 480(±5) minutes post-instillation of assigned IP at Visit 2 (composite score of Nasal Itching, Nasal Congestion, Rhinorrhea and Sneezing)
- Peak Nasal Inspiratory Flow (PNIF) measured pre-ABC® exposure to 8 hours post-instillation of assigned IP at Visit 2 (measured by means of a peak flow meter in L/min)

The first five exploratory endpoints will be analyzed in the same manner as the primary efficacy endpoints. For PNIF, treatment effects will be estimated at 8 hours post-installation of IP at Visit 2, and the statistical hypotheses will be tested using two-sample t-tests assuming equal variances. P-values for all exploratory results will be considered descriptive.

10.1.4 Statistical Hypothesis Testing and Control of Multiplicity

At each of six post-instillation times at Visit 2, the null hypothesis (H_0) is that the difference between the mean redness (or itching) scores for the Test (μ_T) and Standard (μ_S) formulations is 0 points or greater. The alternative hypothesis (H_1) is that the difference is less than 0 points.

$$H_0: \mu_T - \mu_S \geq 0$$
$$H_1: \mu_T - \mu_S < 0$$

The hypotheses above will be tested for each of the six post-instillation times at Visit 2. Each primary endpoint will be summarized by post-instillation of IP time point at Visit 2 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.. 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 and non-optimal compliance 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 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

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 an analysis of covariance model with the primary efficacy variable as the dependent variable, treatment as a factor, and baseline score as a covariate.

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)
- Best Corrected VA at Distance Utilizing an ETDRS chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Vital signs
- Peak Expiratory Flow Rate (PEFR)

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, visual acuity, and vital signs will be presented by treatment at Baseline at Visit 2 with numerical summaries. Change from baseline to Visit 2 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 as well as changes from baseline to Visit 2 in vital sign measurements will be summarized with descriptive statistics for each treatment group.

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 (FAS, 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 physical exams and 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 Visit 2
- Out of window primary endpoint data at any time point of Visit 2
- Use of any prohibited medication potentially affecting the primary endpoint at Visit 2

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 50 subjects in each treatment group yields 95% power to demonstrate each of the following:

- Combo is superior to vehicle in ocular itching (evaluated by the subject)
- Combo is superior to vehicle in ocular redness (evaluated by the Investigator)
- Combo is superior to brimonidine tartrate 0.025% in ocular itching (evaluated by the subject)
- Combo is superior to ketotifen fumarate 0.035% in ocular redness (evaluated by the Investigator)

assuming a one-sided $\alpha = 0.0028$, a true mean difference of 0.65 units and a common standard deviation of 1.0 units at each time point for each measure.

To allow for 10% dropouts, 56 subjects will be randomized in each of the treatment groups.

10.8.3 Multicenter Issues

The study will be conducted at up to 8 investigational centers in the United States 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 four conditions in Section 10.1.1 to declare success for the primary endpoint. 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 10.1.2.

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 must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study.

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 eCRFs 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 eCRFs 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 Electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, 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.

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13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Schedule of Visits and Measurements

Visit	**Visit 1**	**Visit 2**
Day	**-60 to -1**	**1**
PROCEDURE		
General Assessments		
Informed Consent & HIPAA	X	
Demographic Data	X	
Medical & Medication History	X	
Update Medical & Medication History		X
Allergic Skin Test	X	
Urine Pregnancy Test		X
Ocular & Nasal Allergic Signs & Symptoms Assessment		X[8]
Review Incl./Excl. criteria	X	X
Enrollment/Randomization		X
AE Assessment	X	X[9]
TEAE Assessment		X[10]
Allergen Exposure in ABC®		
90 Minute Qualification Exposure		X
8 Hour Post-Treatment Exposure		X
Visual/Systems Exams		
Visual Acuity Utilizing an ETDRS chart	X	X[11]
Slit Lamp Biomicroscopy	X	X[11]
Intraocular Pressure	X	X
Dilated Fundoscopy	X	X
Peak Nasal Inspiratory Flow (PNIF)		X[8]
Peak Expiratory Flow Rate (PEFR)	X	X[8]
Vital Signs (pulse and blood pressure)	X	X
Investigational Product		
In-Office IP Instillation		X
Exit from Clinical Trial		
Study Exit		X

[8] Performed pre- and post-IP instillation during ABC exposure
[9] Prior to first dose of IP
[10] Following first dose of IP
[11] Performed pre- and post-ABC exposure

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 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.

Vital Signs

Each subject will have vital signs assessments (resting blood pressure and pulse) conducted at Visit 1 and Visit 2. Vital signs are to be conducted by a qualified staff member who may be any of the following: a board-certified investigator or sub-investigator, nurse practitioner, registered nurse, or physician's assistant, or trained research coordinator.

Systolic/Diastolic Blood Pressure (mmHg)

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

Pulse (bpm)

Pulse will be measured with the subjects who have been in a resting state (seated) for at least 5 minutes. Pulse may be measured manually by counting for 30 seconds and multiplying by 2 and recording in beats per minute (bpm) or it can be measured digitally and recorded.

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.

Peak Nasal Inspiratory Flow

Peak nasal inspiratory flow (PNIF) readings will be made using an 'in check' inspiratory flow meter with nasal adaptor (Clement Clarke International, England). Measurements will be made in a standing position. Subjects will be instructed to exhale residual volume, place face mask over the mouth and nose to create a good seal around the face mask, and then inhale forcefully to total lung capacity, through the nose, with mouth closed. This maneuver should be a short, sharp inspiratory action of about 1 second in duration. Three measurements will be made. Subjects will be trained to perform the test at Visit 2. Detailed PNIF instructions are provided:

1. Reset the instrument by holding vertically with the mouthpiece up with one hand and tapping lightly onto the other hand such that the small magnetic cylinder dislodges and pushes the red wheel all the way down. When this occurs, invert the instrument and make sure the magnet returns to its resting position.
2. Attach the subject specific filter and mouth piece to the PNIF device. Ensure by asking the subject for their initials.
3. Ask the subject to exhale fully.
4. Ask the subject to press the mask tight against their face forming and air tight seal.
5. Ask the subject, while standing, to hold the device horizontally.
6. Ask the subject to inhale forcibly though their nose as fast and hard as they can.
7. Ensure that the subject is NOT inhaling though their mouth.
8. Repeat the measurement 3 times and record all 3.
9. Place the mask back in the appropriate labeled bag.

Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) will be measured with a hand held peak flow meter (at least 20-30 minutes after subjects have been exposed to room temperature). This test will be conducted for subject safety during all visits according to manufacturer instructions. Three measurements will be made on each occasion. Subjects will be trained to perform the test at Visit 1.

SUBJECT ALLERGEN SCALES

Subject-Evaluated Symptoms (Ocular and Nasal)

Nasal Allergic Symptoms

[redacted]

INVESTIGATOR SCALES

[redacted]

Ora proprietary scales – Not 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 in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	910
Final Date:	31 July 2023

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

[redacted]

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 in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	910
Final Date:	31 July 2023

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

[redacted]

[redacted]

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 in an Allergen BioCube® (ABC®) Clinical Trial in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	910
Final Date:	31 July 2023

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

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

Signed:_____ Date:_____

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