16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Original Protocol Study 17-100-0011 (15 December 2017)

Protocol Amendment Version 1.0 Study 17-100-0011 (28 February 2018)

Protocol Amendment Version 2.0 Study 17-100-0011 (04 April 2018)

Clinical Trial Protocol: 17-100-0011

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Study Phase:	3
Investigational Product Name:	EM-100 topical ophthalmic solution
IND Number:	Not Applicable
Indication:	Allergic Conjunctivitis
Investigators:	Single-center
Sponsor:	EyeMax, LLC 74 Chestnut St. Weston, MA 02493
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:	15 December 2017
Amendment 1:	Not Applicable

Confidentiality Statement

SPONSOR PERSONNEL

President:	[redacted]
Scientific Founder:	[redacted]

ORA PERSONNEL

Medical Monitor:	[redacted]
Chief Medical Officer:	[redacted]
Department Vice President:	[redacted]
Project Lead:	[redacted]

SYNOPSIS

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	17-100-0011
Investigational Product:	EM-100 topical ophthalmic solution
Study Phase:	3
Primary Objective(s):	To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.
Secondary Objective(s):	• To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.
Overall Study Design:	
Structure:	*Screening Period:* At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1. *Treatment Period:* At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100 in the right eye and one of the other

	two treatments in the left eye. A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product.
Duration:	This study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.
Controls:	• Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%, EQ 0.025% Base), ANDA 077200 held by Alcon Pharmaceuticals.
Dosage/ Instillation:	At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below: • EM-100 in right eye and Zaditor® in left eye (N ~ 18) • Zaditor® in right eye and EM-100 in left eye (N ~ 18) • EM-100 in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and EM-100 in left eye (N ~ 6) • Zaditor® in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and Zaditor® in left eye (N ~ 6) A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.
Summary of Visit Schedule:	**Screening Visit (Day -50 to -22):** Screening/ Informed Consent/ Skin Test **Visit 1 (Day -21 ± 3):** Titration CAC **Visit 2 (Day -14 ± 3):** Confirmation CAC

	Visit 3 (Day 1): Enrollment/ Randomization/ In-Office Instillation/ Efficacy CAC/ Study 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 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.
Condition/Disease:	Allergic Conjunctivitis
Inclusion Criteria:	*Each subject must:* 1) be at least 18 years of age at the Screening Visit, of either gender and any race; 2) provide written informed consent and sign the HIPAA form; 3) be willing and able to follow all instructions and attend all study visits; 4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months; 5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period; 7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be

	lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart; 9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1; 10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.
Exclusion Criteria:	*Each subject <u>must not</u>:* 1) have known contraindications or sensitivities to the use of the investigational product or any of its components; 2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye); 3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months; 4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

	5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit; 6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study: **7 Days** • systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.* **14 Days** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **45 Days** • depot-corticosteroids; **2 Months** • immunosuppressive or cancer chemotherapeutic agents; *Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.* 7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels

	could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens; 8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye; 9) have planned surgery (ocular or systemic) during the trial period or within 30 days after; 10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial; 11) be a female who is currently pregnant, planning a pregnancy, or lactating.
Study Formulations and Formulation Numbers:	• EM-100 topical ophthalmic solution • Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)
Evaluation Criteria:	
Efficacy Measures and Endpoints:	**Primary:** • Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. **Secondary:** • Conjunctival redness evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0 to 4 scale, allowing half unit increments) at Visit 3.
Safety Measures:	• Adverse Events (reported, elicited, and observed) • Best Corrected Visual Acuity (BCVA) at Distance • Slit Lamp Biomicroscopy

General Statistical Methods and Types of Analyses

The following analysis populations will be defined:

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

Per Protocol Set – The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

Safety Analysis Set – The safety population includes all subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

Sample Size:

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.

The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

Primary Efficacy Analyses:

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

Secondary Efficacy Analyses:

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority tests of the primary endpoint. The secondary endpoint will be analyzed for the ITT population with observed data only and for the PP population with observed data only.

Safety Analyses:

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

Summary of Known and Potential Risks and Benefits to Human Subjects

Known and potential risks of ketotifen fumarate ophthalmic solution (0.035%) include ocular burning/stinging/irritation, headache, rhinorrhea, and photophobia. Benefits include relief and prevention of ocular itching associated with allergic conjunctivitis.

Refer to the Zaditor® Package Insert regarding risks and benefits to human subjects.

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LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DHHS	Department of Health and Human Services
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug application
IP	investigational product
IRB	institutional review board
ITT	intent to treat
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
ND	not done
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PE	polyethylene
PP	per protocol
SAE	serious adverse event
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
VA	visual acuity

1 INTRODUCTION

Allergies affect approximately 15% of the global population and up to 30% of the U.S. population [(1)]. Allergic reactions can vary from a mild, self-limiting condition to a debilitating condition that significantly impairs the quality of life. Allergic conjunctivitis is generally considered a type 1 hypersensitivity reaction, and is the most prevalent allergic condition, representing about a third of all allergic disorders.

The physiologic basis for allergic conjunctivitis is multifactorial and involves both an early acute phase triggered by mast cell degranulation and release of histamine, and a late phase involving various pro-inflammatory mediators [(2)]. Histamine is the primary mediator responsible for the early phase reaction that triggers itching, vasodilation, and vascular leakage leading to ocular redness, chemosis, and blepharitis. The early phase response occurs within minutes to hours following allergen exposure. The itching associated with the early phase allergic reaction has been shown to peak at ~ 5-7 minutes after allergen provocation, which coincides with mast-cell degranulation. Mast cells also synthesize and release cytokines, chemokines, and growth factors that initiate a cascade of inflammatory events leading to a late-phase reaction involving a variety of pro-inflammatory mediators including prostaglandins, leukotrienes, cytokines, and interleukins and characterized by recruitment of eosinophils, neutrophils, and subsequent lymphocytes and macrophages into the conjunctival tissues [(3, 4)].

Ketotifen is a widely effective therapy for the management of ocular allergies. It has demonstrated rapid onset (≤ 15 minutes) and long duration of action (≥ 8 hours) after conjunctival allergen challenge (CAC)[(5, 6)]. Ketotifen fumarate ophthalmic solution 0.035% was found to be safe, well tolerated, and effective for the prevention of the signs and symptoms associated with allergic conjunctivitis in multiple CAC studies[(7-12)]. In an environmental setting, ketotifen fumarate ophthalmic solution 0.035% was found to safely and effectively reduce seasonal allergic conjunctivitis signs and symptoms and prevent recurrence[(13)].

Ketotifen fumarate ophthalmic solution 0.035% (Zaditor®/Zaditen®; Novartis Ophthalmics) is approved in the United States and Canada for the temporary prevention of ocular itching due to allergic conjunctivitis at a dose of one drop in the affected eye twice daily (every 8-12 hours)[(14)]. In 2006, ketotifen fumarate ophthalmic drops 0.035% (ketotifen 0.025%; Alaway®; Bausch and Lomb, Inc., and Zaditor®; Novartis Ophthalmics) were approved by the United States Food and Drug Administration (FDA) for over-the-counter use, with the indication of temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander, at an approved dose of one drop in the affected eye twice daily (every 8-12 hours)[(15)].

EM-100 contains ketotifen ophthalmic solution (0.025%) as a non-preserved formulation in single-dose vials. This is a single-center, randomized, double-masked study to establish the therapeutic equivalence of EM-100 to Zaditor® (ketotifen fumarate

ophthalmic drops 0.035%). EM-100 will need to show non-inferiority to Zaditor® in the treatment of ocular itching following CAC (15 minutes following study medication instillation). The vehicle is included for assay validation.

2 STUDY OBJECTIVES

Primary:

- To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.

Secondary:

- To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis.
- To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis
- To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.

3 CLINICAL HYPOTHESES

The clinical hypotheses are:

- EM-100 is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC 15 minutes following product instillation.
- EM-100 is non-inferior to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.
- Zaditor® is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.

4 OVERALL STUDY DESIGN

This is a single-center, randomized, double-masked, contralateral eye study comparing topical EM-100 with Zaditor® and the vehicle of EM-100 in subjects with allergic conjunctivitis. At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-

CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1.

At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below:

- EM-100 in right eye and Zaditor® in left eye (N ~ 18)
- Zaditor® in right eye and EM-100 in left eye (N ~ 18)EM-100 in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and EM-100 in left eye (N ~ 6)
- Zaditor® in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and Zaditor® in left eye (N ~ 6)

A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.

5.2 Study Population Characteristics

5.3 Inclusion Criteria

Each subject must:

1) be at least 18 years of age at the Screening Visit, of either gender and any race;
2) provide written informed consent and sign the HIPAA form;
3) be willing and able to follow all instructions and attend all study visits;
4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months;
5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6);

6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period;
7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1;
10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.

5.4 Exclusion Criteria

Each subject <u>must not</u>:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study:

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.*

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents;

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.

7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye;
9) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
11) be a female who is currently pregnant, planning a pregnancy, or lactating.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Any female will be removed from the study should she become pregnant during the course of the study, and she will undergo a pregnancy test at her exit visit for confirmation. The pregnancy test must be confirmed by two (2) additional tests and confirmed by the principal investigator (or sub-investigator if the principal investigator is not present). If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The Investigator will follow-up and document the outcome of the pregnancy and provide a copy of the documentation to the sponsor. The Ora Pregnancy Report Form will be used to report a pregnancy and follow-up.

Reason for withdrawal will be included in the eCRF, and all efforts should be made to schedule the subject for an Exit Visit to complete exit procedures. Any subject who is withdrawn for the study because of an AE will be followed until AE is resolved or as clinically required, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

Sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.5).

6 STUDY PARAMETERS

6.1 Efficacy Measures and Endpoints

6.1.1 Primary Efficacy Endpoint(s)

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3.

6.1.2 Secondary Efficacy Endpoints(s)

- Conjunctival redness evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0 to 4 scale, allowing half unit increments) at Visit 3.

6.1.3 Criteria for Effectiveness

This therapeutic equivalence study is designed to evaluate the relative efficacy of EM-100 topical ophthalmic solution compared to vehicle and Zaditor® in the treatment of

ocular itching at each designated time point post-CAC at Visit 3 (Day 1, 15-minute onset).

Although this study is being referred to as a "bioequivalence" or "therapeutic equivalence" study, it is in fact a non-inferiority study and all statistical testing will determine whether EM-100 is non-inferior to the reference drug, Zaditor®. Vehicle is included in this study in order to validate the assay.

To demonstrate non-inferiority for ocular itching compared to Zaditor®, EM-100 topical ophthalmic solution needs to show itching scores no worse than 0.75 units (using the same scale) worse than Zaditor® as determined by a one-sided test at alpha = 0.025 for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC.

To demonstrate superiority for ocular itching compared to vehicle, EM-100 topical ophthalmic solution needs to show clinical superiority over vehicle by at least 0.5 units of a 5 point scale for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC, and at least 1 unit for the majority (2:3) of the post-CAC time points. Statistically significant differences at two-sided alpha levels of 0.05 are also required for each post-CAC time point. This statistical significance is expected given the clinical superiority requirements above.Primary and secondary analyses will be tested using a fixed sequence, as described in Section 10.7.

6.2 Safety Measures

- Adverse Events (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) at Distance
- Slit Lamp Biomicroscopy

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)

- EM-100 topical ophthalmic solution
- Vehicle of EM-100 topical ophthalmic solution
- Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)

7.1.2 Instructions for Use and Administration

- This trial requires additional attention in order to preserve masking of study treatment. There will be a total of 485 identical appearing kits containing all three treatments labeled A, B, and C. Once the kits arrive at the site, a designated staff

member will randomly select 65 kits to be used for the trial. The remaining 420 kits will be identified and stored as retains. Both EM-100 and the vehicle of EM-100 will be identical in appearance as single use vials, while the reference product, Zaditor®, will be in its original bottle. All individual kits will be sealed with tamper evident tape and the sites will be instructed to not open the kits upon receipt of shipment. At no point during the trial (until database lock) will site staff or monitors be allowed to open the kits unless it is the designated "unmasked" technicians. These technicians will ensure that opening of the kits is done in a manner to prevent the other staff and subjects from seeing the investigational product. For each subject treatment will be administered by eye according to a randomization list which will be sent to the site in a sealed envelope and opened at Visit 3 by the unmasked technicians. Following Visit 3 dosing, the technicians will reseal the kits and randomization list envelope using tamper evident tape and return the kits to storage. The sealed randomization list envelope will be filed in the investigator's study file.

- At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100. A randomization list will inform the technicians which corresponding letter treatment should be instilled in the right eye and which one should be instilled in the left eye.

- A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC.

- The pre-specified unmasked technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site. Care will be taken to hide the container (vial or bottle) from the subject. Dosing will occur in a room where no other subjects, staff, or investigators will observe the instillation.

- Investigational product must be stored in a secure area of the clinical site, accessible only to the Investigator(s) or designees at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

- In accordance with 21CFR §320.38 and §320.63, samples of both the test article (EM-100) and reference listed drug (Zaditor®) will be retained and stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel.

7.2 Other Study Supplies

The following supplies will be supplied and/or reconstituted by Ora, Inc.:

- Pregnancy tests (Clarity HCG, RAC Medical Boca Raton, FL).
- The allergens used for skin testing and the conjunctival allergen challenge (cat dander, dog dander, dust mite, cockroach, meadow fescue, rye grass, Bermuda grass, Kentucky bluegrass, Timothy grass, ragweed, white birch, oak, and maple).
- Relief drops (OTC antihistamine/vasoconstrictor combination products).

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 (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board. Failure to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to return to the clinic for study Visits 1, 2, and 3.

Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

8.1.3 Washout Intervals

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

72 Hours

- contact lenses;

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizers, H_1 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);

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents.

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

8.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion criteria and none of the exclusion criteria prior to Visit 3 to be enrolled in this 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. 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 treatment groups, and to enhance the validity of statistical comparisons.

Once a subject meets qualification criteria at Visit 3 (Day 1), he/she will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.

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

- contact lenses
- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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)
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers
- depot-corticosteroids
- immunosuppressive or cancer chemotherapeutic agents

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

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 the Screening Visit.

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

Currently marketed over-the-counter anti-allergy eye drops (i.e., anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained personnel at the end of Visits 1, 2, and 3 after all evaluations are completed.

8.2.3 Special Diet or Activities

Not Applicable.

8.3 Examination Procedures

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

8.3.1.1 SCREENING VISIT (Day -50 to -22): Screening/ Informed Consent/ Skin Test

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

  Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

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

- *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 45 days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 45 days prior to Visit 1.

- *Review of Inclusion/Exclusion Criteria:* Confirm if subject needs to washout from any current medications and instruct he/she to follow the appropriate washout time periods (refer to Section 8.1.3)

- *Adverse Event Query*

- *Schedule Visit 1:* Qualifying subjects will be scheduled for Visit 1.

8.3.1.2 VISIT 1 (Day -21 ± 3): Titration CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (for females of childbearing potential):* Females of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled.

- *Initial Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify.

- *Initial Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess initial ocular itching and conjunctival redness using the Ora-CAC® scales (see **Appendix 2**). Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score) will be excluded.

- *Initial Slit Lamp Biomicroscopy:* A slit lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions (see **Appendix 2**). Findings of abnormality which are not exclusionary should be recorded as Medical History.

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

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

  If the subject fails to react within 10 (±2) minutes, increasingly concentrated doses may be instilled bilaterally at approximately ten-minute intervals until a positive reaction is elicited. If increasing doses are required (i.e., for insufficient bilateral itching and/or redness as evaluated by a trained technician or the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen (up to maximum concentration of 5000 AU), other allergens to which the subject is sensitized may be used starting at the lowest dose.

- *Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Upon completion of the initial titration CAC, subjects will receive an ocular examination by the Investigator to evaluate conjunctival redness and confirm the subject's qualification. Subjects will be asked to assess their ocular itching.

  A positive CAC at Visit 1 is defined as a score of $\geq$ 2 for redness in the conjunctival vessel bed of each eye and $\geq$ 2 for itching in each eye within 10 (±2) minutes of receiving that dose of allergen. Any subject who fails to test positively will be excluded from the study.

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

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) by trained study personnel as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 2:* Qualifying subjects will be scheduled to return to the office in one (1) week for Visit 2.

8.3.1.3 VISIT 2 (Day -14 ± 3): Confirmation CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of +0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Pre-CAC Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess pre-CAC ocular itching and conjunctival redness using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score in either eye) will be excluded.

- *Slit Lamp Biomicroscopy*

- *Review of Inclusion/Exclusion Criteria*

- *Confirmation CAC*: For each qualified subject, one drop of the allergen solution, of the same, final dose that elicited a positive reaction at Visit 1, will be administered bilaterally.

- *Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Assessments of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following

allergen challenge. Assessments of conjunctival redness will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**). If the subject fails to react positively (i.e., ≥2 ocular itching and ≥2 redness in the conjunctival vessel bed) in both eyes in at least two (2) out of the first three (3) time points[1], he/she will be excluded from the study.

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 3:* Subjects will be asked to return to the office two (2) weeks later for Visit 3.

8.3.1.4 VISIT 3 (Day 1): Enrollment/Randomization/ In-Office Instillation/ Efficacy CAC/ Study Exit

- *Update of Medical/Medication History*

- *Adverse Event Query*

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

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Pre-CAC Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess pre-CAC ocular itching and conjunctival redness using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as >1 redness in conjunctival bed or the presence of any itching in either eye) will be excluded.

- *Slit Lamp Biomicroscopy*

- *Review of Inclusion/Exclusion Criteria*

[1] not necessarily at the same time point

- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria and qualify to continue in the study will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.

- *Investigational Product Instillation:* A trained study technician will instill one drop of the assigned treatment in the right eye and one drop of the assigned treatment in the left eye, according to the directions for use. The investigational product kit number and the time of instillation will be recorded. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.

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

- *Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Assessments of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of conjunctival redness will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**).

- *Exit Slit Lamp Biomicroscopy*

- *Exit Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Study Exit:* Subjects will be exited from the study.

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

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document

the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

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

If a subject is discontinued at a scheduled study visit (i.e. Visit 3), the remaining assessments should be captured on the Unscheduled Visit/ Early Exit Visit pages of the source document and corresponding eCRF. Subjects who screen fail (Screening Visits or Visits 1, 2, or 3) may be scheduled for the Unscheduled Visit at the Investigator's discretion due to follow-up of an ongoing AE.

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 in order 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:

- Assessment of Adverse Events
- Assessment of Concomitant Medications
- Visual Acuity Utilizing an ETDRS chart
- Urine Pregnancy Test (for females of childbearing potential)
- Slit lamp Biomicroscopy

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

8.5 Compliance with Protocol

Subjects who are inappropriately enrolled or no longer fulfill the study eligibility criteria 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 by asking subjects if they changed their dosing regimen since their previous visit. The response will be recorded in the source document and on the eCRF at Visits 1, 2, and 3.

All protocol violations, regardless of causation, will be recorded in the subject's source document as well as eCRF. Major protocol violations will be recorded in the subject's source document, entered in the eCRF, and reported to the IRB, as per the applicable regulations.

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. Subjects who are discontinued from the study will not be replaced.

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 study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.

8.9 Monitoring and Quality Assurance

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

confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

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

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

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

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
  - *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
  - *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE event include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study

population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

Adverse events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

  Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

Collection of AEs/SAEs will begin at the time of informed consent.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate eCRFs. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs. All SAEs, regardless of expectedness or relationship to the IP, will be reported to the FDA as soon as possible but no later than 15 calendar days after becoming aware of the event.

Contact information for reporting SAEs:

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.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

AEs will be followed until:

- Resolution (return to baseline status or to "normal")
- Stabilization of the event has occurred (no improvement or worsening expected by the investigator)
- Event is otherwise explained, regardless of whether the subject is still participating in the study
- Principal investigator determines, for events that do not end (i.e., metastasis), the condition to be chronic. The event can be determined to be resolved or resolved with sequelae.

The Investigator will follow unresolved adverse events to resolution until the subject is lost to follow-up or until the adverse event is otherwise explained. If the subject is lost to follow-up, the Investigator should make three (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 adverse events identified on the last scheduled contact must be recorded on the AE eCRF with the status noted and be followed as aforementioned.

If the Investigator becomes aware of any new information regarding a Serious Adverse Event (i.e., resolution, change in condition, or new treatment), a new Serious Adverse Event/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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Study Populations

10.1.1 Intent-to-Treat Population

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

10.1.2 Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

10.1.3 Safety Population

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

10.2 General Imputation Methods

Missing data is not expected in this single, post-randomization visit study. However, if missing data does result, missing data for the primary efficacy variable will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation techniques on the ITT population. A separate model will be fit for each time point. The model will include variables for treatment, time appropriate baseline measure and response measure.

For sensitivity analysis, the ITT population will also be analyzed using observed data only.

10.3 Statistical Hypotheses

The statistical hypotheses for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® are as follows:

PRIMARY:

H_{01}: Ocular itching scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a1}: Ocular itching scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

SECONDARY:

Conditional upon H_{01} being rejected, the statistical hypothesis for the superiority test between EM-100 ophthalmic solution and vehicle solution will be tested as follows:

H_{02}: There is no difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a2}: There is a difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01} and H_{02} being rejected, the statistical hypothesis for the superiority test between Zaditor® and vehicle solution will be tested as follows:

H_{03}: There is no difference in ocular itching scores between Zaditor® and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a3}: There is a difference in ocular itching scores between Zaditor® and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01}, H_{02}, and H03 being rejected, the statistical hypothesis for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® will be tested as follows:

H_{04}: Conjunctival redness scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a4}: Conjunctival redness scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

10.4 Sample Size

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.
The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show

a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

10.5 Primary Efficacy Analyses

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

As an additional sensitivity analysis, a general linear model will be run with treatment, time point, and time appropriate baseline as covariates for adjustment, accounting for repeated measurements within each eye as well as the correlation within subjects between eyes. LS Means and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% CIs, will be calculated from this linear model.

The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population using the multiple imputation MCMC method for missing data (if missing data arises) as described in Section 10.2. Sensitivity or supportive analyses will be performed using observed data only for both the ITT and PP populations.

10.6 Secondary Efficacy Analyses

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority tests of the primary endpoint. The secondary endpoint will be analyzed for the ITT population with observed data only and for the PP population with observed data only.

The superiority of EM-100 versus vehicle and of Zaditor® versus vehicle will also be tested as supportive analyses.

10.7 Adjustment for Multiplicity

The primary and secondary analyses will be tested in a fixed sequence to maintain the study-wide Type I error for these analyses. The primary analysis testing non-inferiority of EM-100 versus Zaditor® will be performed first. In order to perform the secondary analysis testing the superiority of EM-100 over vehicle, the primary analysis must first be successful. Conditional upon both the primary analysis and the first secondary analysis being successful, the second secondary analysis comparing Zaditor® and the vehicle of EM-100 will be performed. The fixed sequence testing will proceed as follows:

1) Primary analysis of the primary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for ocular itching at Visit 3
2) Secondary analysis of the primary endpoint: Testing superiority of EM-100 vs. vehicle for ocular itching at Visit 3
3) Secondary analysis of the primary endpoint: Testing superiority of Zaditor® vs. vehicle for ocular itching at Visit 3
4) Analysis of the secondary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for conjunctival redness at Visit 3

In addition, statistical success must be met for all three post-CAC time points for each analysis. Proceeding to the next hierarchical analysis requires all three post-CAC time points are statistically significant for the previous analyses. Therefore, no adjustments for multiplicity are required.

10.8 Demographic and Baseline Medical History

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

10.9 Safety Analysis

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

10.10 Interim Analysis

No interim analyses are planned.

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 Harmonization (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 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 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 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 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

Each kit will contain the 3 treatments labeled A, B, and C. The EM-100 and vehicle will consist of five single use 0.4mL vials packaged in an aluminum pouch. Zaditor® will be in its original bottle with the label removed. A label containing the letter A, B, or C will be on the bottles of Zaditor® and the pouches of both EM-100 and vehicle of EM-100. There will be 485 kits created. Kits will be labeled on the outside with a kit number ranging from 001-485. Each kit will be sealed with tamper evident tape.

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. Kits will be left unopened until the authorized unmasked technicians open the assigned kit for administration to each randomized subject. Following administration to the subject, the technicians will return the product to the kit and seal the kit with tamper evident tape.

Investigational product must be stored at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

Upon receiving the shipment of IP, the investigator or his/her designee will select at random the appropriate number of units to be designated as the retain samples. A label will be affixed to the designated units to identify these as “retain samples.” These retain samples will not be assigned to study subjects for clinical use. All of the retain samples will be stored in a secure area accessible only to the investigator and his/her designees. The retain samples will be segregated from the investigational product to be assigned to study subjects for clinical use, but will be stored in the same area and under the same conditions for the duration of the study.

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 administered to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP. Note only the kit number and number of kits will be tallied. The kits will remain sealed prior to and following Visit 3. There will be no counting of individual IP inside the kit.

The investigator must also keep an accurate accounting of the retain samples and must properly document the inventory.

11.5.4 Return or Disposal of Investigational Product

All IP used in the clinical trial will be returned to the sponsor (or their designee) or destroyed at the study site. The return or disposal of IP will be specified in writing. All of the retain samples will be shipped to a third party vendor for long-term storage.

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

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

Procedure	Screening Visit	Visit 1	Visit 2	Visit 3
	Day -50 to -22	Day -21 ± 3	Day -14 ± 3	Day 1
Informed Consent/HIPAA[1]	X			
Demographic Data	X			
Medical/Medication History	X			
Medical/Medication History Update		X	X	X
Allergic Skin Test	X			
Visual Acuity		X	X	X
Urine Pregnancy Test (for females of childbearing potential)[2]		X		X
Assessments of Ocular Itching and Conjunctival Redness		X	X	X
Slit Lamp Biomicroscopy		X	X	X
Titration Conjunctival Allergen Challenge		X		
Confirmation Conjunctival Allergen Challenge			X	
Enrollment/Randomization				X
Investigational Product Instillation[3]				X
Efficacy Conjunctival Allergen Challenge				X
Relief Drop Instillation		X	X	X
Adverse Event Query	X	X	X	X
Exit from Study				X

[1] Informed consent must be signed before any study-related procedure can be performed.
[2] 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 surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[3] Instilled 15(+1) minutes prior to CAC

APPENDIX 2: EXAMINATION PROCEDURES, TESTS,

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 only the 'R' charts, and the right eye should be tested first. 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.

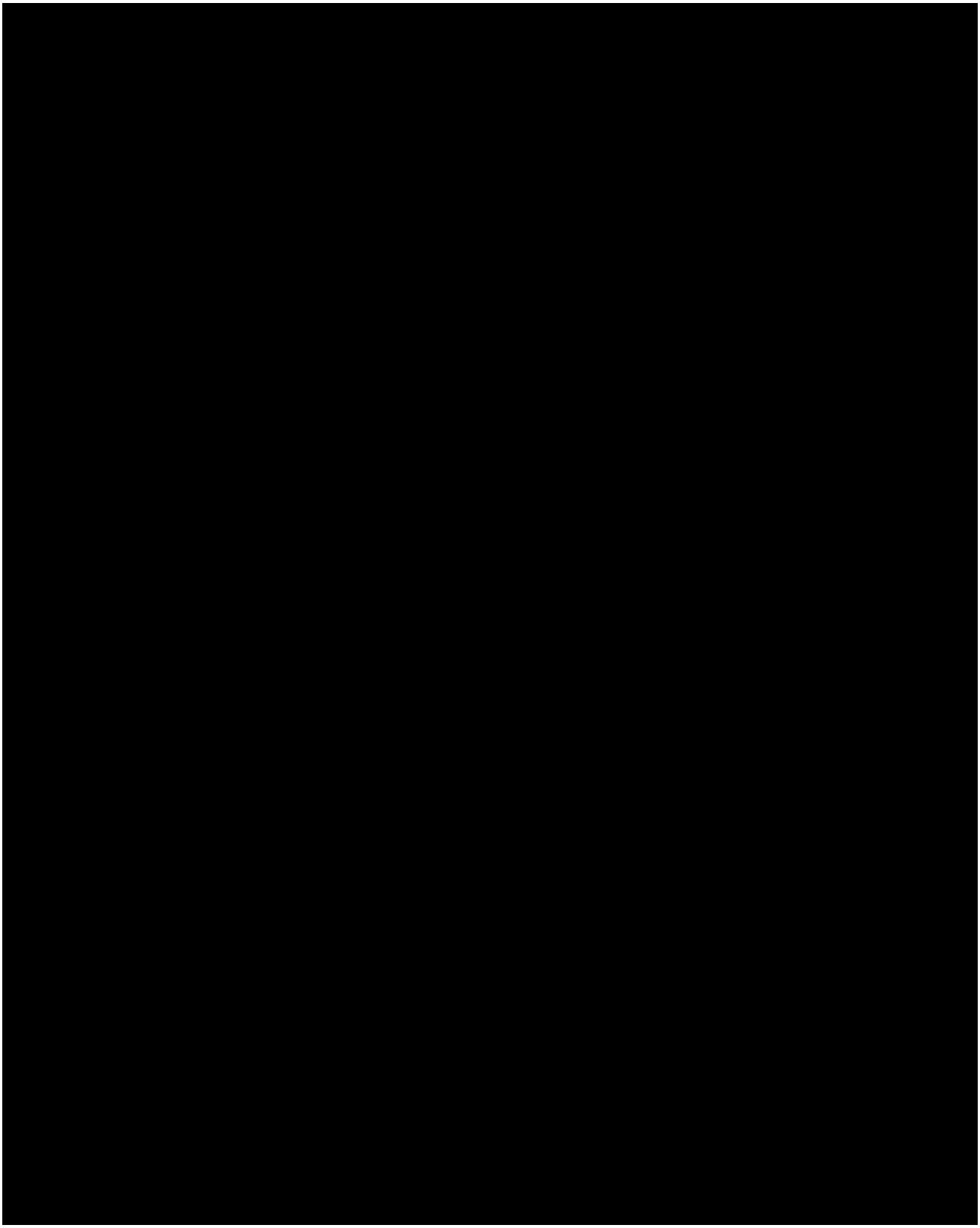
In order to provide standardized and well-controlled assessments of VA during the study, all VA assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a subject forgets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



APPENDIX 3: PACKAGE INSERT

Drug Facts

Active ingredients
Ketotifen (0.025%)

(equivalent to ketotifen fumarate 0.035%)

Purpose
Antihistamine

Uses
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

Warnings
For external use only

Do not use
- if solution changes color or becomes cloudy
- if you are sensitive to any ingredient in this product
- to treat contact lens related irritation

When using this product
- do not touch tip of container to any surface to avoid contamination
- remove contact lenses before use
- wait at least 10 minutes before reinserting contact lenses after use
- replace cap after each use

Stop use and ask doctor if you experience any of the following:
- eye pain
- changes in vision
- redness of the eyes
- itching worsens or lasts for more than 72 hours

Keep out of reach of children.

If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- **Adults and children 3 years of age and older:**
  Put 1 drop in the affected eye(s) twice daily, every 8–12 hours, no more than twice per day.
- **Children under 3 years of age:** Consult a doctor.

Other information

- Only for use in the eye.
- Store between 4°–25°C (39°–77°F).

Inactive ingredients

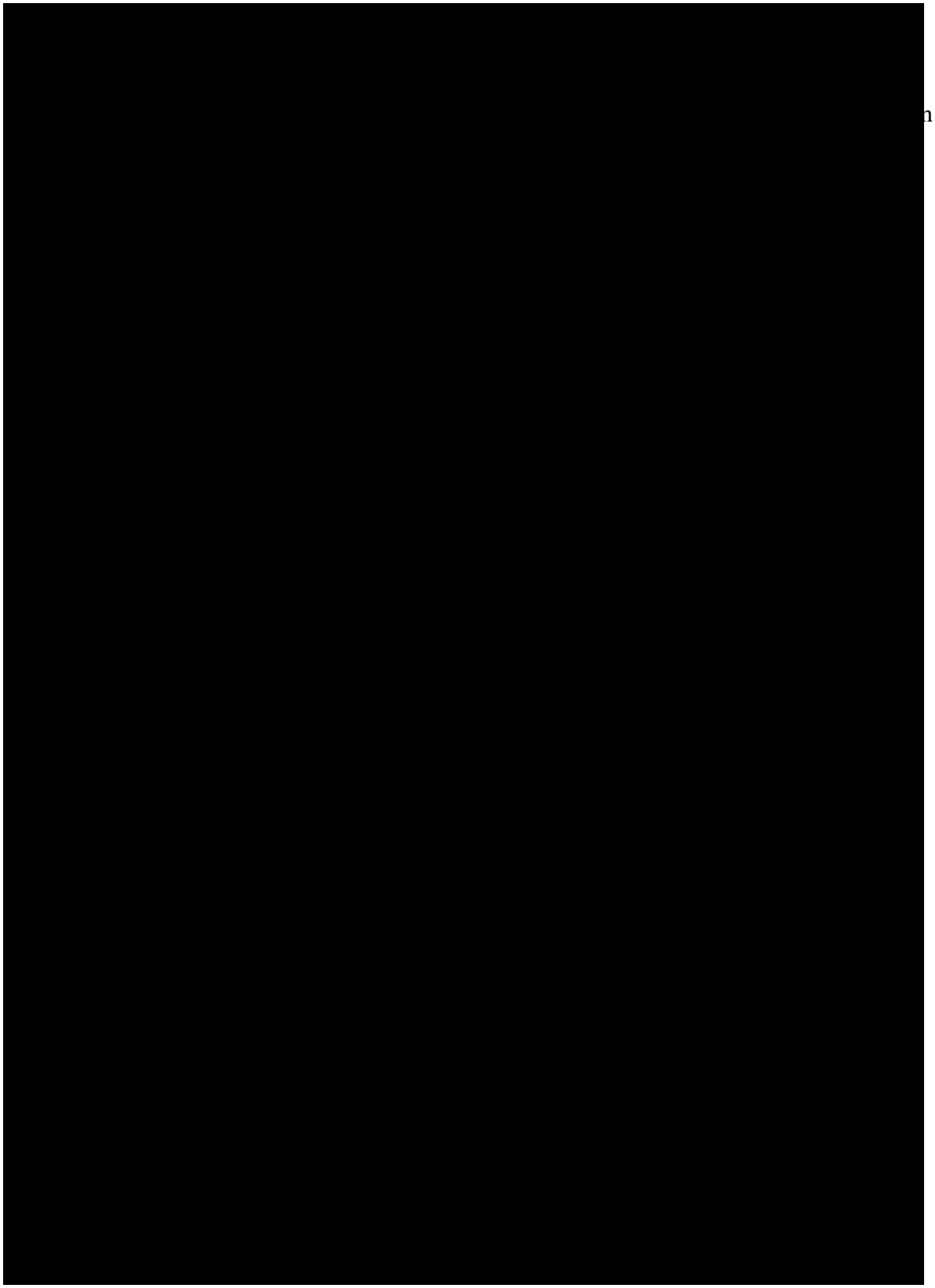
benzalkonium chloride 0.01%, glycerol, purified water, sodium hydroxide, and/or hydrochloric acid

APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT SUMMARY

Not Applicable.



[redacted]

EM-100 Topical Ophthalmic Solution
Clinical Trial Protocol: 17-100-0011
EyeMax, LLC
Final 1.0/15Dec2017

APPENDIX 8: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	17-100-0011
Final Date:	15 December 2017

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>
<enter phone number>

Clinical Trial Protocol: 17-100-0011

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Study Phase:	3
Investigational Product Name:	EM-100 topical ophthalmic solution
IND Number:	Not Applicable
Indication:	Allergic Conjunctivitis
Investigators:	Single-center
Sponsor:	EyeMax, LLC 74 Chestnut St. Weston, MA 02493
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:	15 December 2017
Amendment 1:	28 February 2018

Confidentiality Statement

SPONSOR PERSONNEL

President:	[redacted]

ORA PERSONNEL

Medical Monitor:	[redacted]
Chief Medical Officer:	[redacted]
Department Vice President:	[redacted]
Project Lead:	[redacted]

SYNOPSIS

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	17-100-0011
Investigational Product:	EM-100 topical ophthalmic solution
Study Phase:	3
Primary Objective(s):	To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.
Secondary Objective(s):	• To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.
Overall Study Design:	
Structure:	*Screening Period:* At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1. *Treatment Period:* At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100 in the right eye and one of the other

	two treatments in the left eye. A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product.
Duration:	This study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.
Controls:	• Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%, EQ 0.025% Base), ANDA 077200 held by Alcon Pharmaceuticals.
Dosage/ Instillation:	At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below: • EM-100 in right eye and Zaditor® in left eye (N ~ 18) • Zaditor® in right eye and EM-100 in left eye (N ~ 18) • EM-100 in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and EM-100 in left eye (N ~ 6) • Zaditor® in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and Zaditor® in left eye (N ~ 6) A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.
Summary of Visit Schedule:	**Screening Visit (Day -50 to -22):** Screening/ Informed Consent/ Skin Test **Visit 1 (Day -21 ± 3):** Titration CAC **Visit 2 (Day -14 ± 3):** Confirmation CAC

	Visit 3 (Day 1): Enrollment/ Randomization/ In-Office Instillation/ Efficacy CAC/ Study 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 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.
Condition/Disease:	Allergic Conjunctivitis
Inclusion Criteria:	*Each subject must:* 1) be at least 18 years of age at the Screening Visit, of either gender and any race; 2) provide written informed consent and sign the HIPAA form; 3) be willing and able to follow all instructions and attend all study visits; 4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months; 5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period; 7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be

	lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart; 9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1; 10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.
Exclusion Criteria:	*Each subject must not:* 1) have known contraindications or sensitivities to the use of the investigational product or any of its components; 2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye); 3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months; 4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

	5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit; 6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study: **7 Days** • systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.* **14 Days** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **45 Days** • depot-corticosteroids; **2 Months** • immunosuppressive or cancer chemotherapeutic agents; *Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.* 7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels

	could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens; 8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye; 9) have planned surgery (ocular or systemic) during the trial period or within 30 days after; 10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial; 11) be a female who is currently pregnant, planning a pregnancy, or lactating.
Study Formulations and Formulation Numbers:	• EM-100 topical ophthalmic solution • Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)
Evaluation Criteria:	
Efficacy Measures and Endpoints:	**Primary:** • Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. **Secondary:** The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC at Visit 3: • Conjunctival redness evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Ciliary redness evaluated by the investigator (0 to 4

	scale, allowing half unit increments) • Episcleral redness evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Chemosis evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Eyelid swelling evaluated by the subject (0 to 3 scale, NOT allowing half unit increments) • Tearing/watery eyes evaluated by the subject (0 to 4 scale, NOT allowing half unit increments) • Ocular mucous discharge evaluated by the subject CAC (absent/present) • Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)
Safety Measures:	• Adverse Events (reported, elicited, and observed) • Best Corrected Visual Acuity (BCVA) at Distance • Slit Lamp Biomicroscopy

General Statistical Methods and Types of Analyses

The following analysis populations will be defined:

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

Per Protocol Set – The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

Safety Analysis Set – The safety population includes all subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

Sample Size:

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.

The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

Primary Efficacy Analyses:

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes

post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

Secondary Efficacy Analyses:

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority tests of the primary endpoint. Secondary endpoints (Ciliary redness, Episcleral redness, Chemosis, Eyelid Swelling, Tearing, Ocular Mucous Discharge, Rhinorrhea, Nasal Pruritus, Ear/Palate Pruritus, Nasal Congestion) will be analyzed as supportive analyses.

Safety Analyses:

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

Summary of Known and Potential Risks and Benefits to Human Subjects

Known and potential risks of ketotifen fumarate ophthalmic solution (0.035%) include ocular burning/stinging/irritation, headache, rhinorrhea, and photophobia. Benefits include relief and prevention of ocular itching associated with allergic conjunctivitis.

Refer to the Zaditor® Package Insert regarding risks and benefits to human subjects.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DHHS	Department of Health and Human Services
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug application
IP	investigational product
IRB	institutional review board
ITT	intent to treat
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
ND	not done
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PE	polyethylene
PP	per protocol
SAE	serious adverse event
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
VA	visual acuity

1 INTRODUCTION

Allergies affect approximately 15% of the global population and up to 30% of the U.S. population [(1)]. Allergic reactions can vary from a mild, self-limiting condition to a debilitating condition that significantly impairs the quality of life. Allergic conjunctivitis is generally considered a type 1 hypersensitivity reaction, and is the most prevalent allergic condition, representing about a third of all allergic disorders.

The physiologic basis for allergic conjunctivitis is multifactorial and involves both an early acute phase triggered by mast cell degranulation and release of histamine, and a late phase involving various pro-inflammatory mediators [(2)]. Histamine is the primary mediator responsible for the early phase reaction that triggers itching, vasodilation, and vascular leakage leading to ocular redness, chemosis, and blepharitis. The early phase response occurs within minutes to hours following allergen exposure. The itching associated with the early phase allergic reaction has been shown to peak at ~ 5-7 minutes after allergen provocation, which coincides with mast-cell degranulation. Mast cells also synthesize and release cytokines, chemokines, and growth factors that initiate a cascade of inflammatory events leading to a late-phase reaction involving a variety of pro-inflammatory mediators including prostaglandins, leukotrienes, cytokines, and interleukins and characterized by recruitment of eosinophils, neutrophils, and subsequent lymphocytes and macrophages into the conjunctival tissues [(3, 4)].

Ketotifen is a widely effective therapy for the management of ocular allergies. It has demonstrated rapid onset (≤ 15 minutes) and long duration of action (≥ 8 hours) after conjunctival allergen challenge (CAC)[(5, 6)]. Ketotifen fumarate ophthalmic solution 0.035% was found to be safe, well tolerated, and effective for the prevention of the signs and symptoms associated with allergic conjunctivitis in multiple CAC studies[(7-12)]. In an environmental setting, ketotifen fumarate ophthalmic solution 0.035% was found to safely and effectively reduce seasonal allergic conjunctivitis signs and symptoms and prevent recurrence[(13)].

Ketotifen fumarate ophthalmic solution 0.035% (Zaditor®/Zaditen®; Novartis Ophthalmics) is approved in the United States and Canada for the temporary prevention of ocular itching due to allergic conjunctivitis at a dose of one drop in the affected eye twice daily (every 8-12 hours)[(14)]. In 2006, ketotifen fumarate ophthalmic drops 0.035% (ketotifen 0.025%; Alaway®; Bausch and Lomb, Inc., and Zaditor®; Novartis Ophthalmics) were approved by the United States Food and Drug Administration (FDA) for over-the-counter use, with the indication of temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander, at an approved dose of one drop in the affected eye twice daily (every 8-12 hours)[(15)].

EM-100 contains ketotifen ophthalmic solution (0.025%) as a non-preserved formulation in single-dose vials. This is a single-center, randomized, double-masked study to establish the therapeutic equivalence of EM-100 to Zaditor® (ketotifen fumarate

ophthalmic drops 0.035%). EM-100 will need to show non-inferiority to Zaditor® in the treatment of ocular itching following CAC (15 minutes following study medication instillation). The vehicle is included for assay validation.

2 STUDY OBJECTIVES

Primary:

- To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.

Secondary:

- To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis.
- To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis
- To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.

3 CLINICAL HYPOTHESES

The clinical hypotheses are:

- EM-100 is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC 15 minutes following product instillation.
- EM-100 is non-inferior to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.
- Zaditor® is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.

4 OVERALL STUDY DESIGN

This is a single-center, randomized, double-masked, contralateral eye study comparing topical EM-100 with Zaditor® and the vehicle of EM-100 in subjects with allergic conjunctivitis. At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-

CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1.

At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below:

- EM-100 in right eye and Zaditor® in left eye (N ~ 18)
- Zaditor® in right eye and EM-100 in left eye (N ~ 18)EM-100 in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and EM-100 in left eye (N ~ 6)
- Zaditor® in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and Zaditor® in left eye (N ~ 6)

A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.

5.2 Study Population Characteristics

5.3 Inclusion Criteria

Each subject must:

1) be at least 18 years of age at the Screening Visit, of either gender and any race;
2) provide written informed consent and sign the HIPAA form;
3) be willing and able to follow all instructions and attend all study visits;
4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months;
5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6);

6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period;
7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1;
10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.

5.4 Exclusion Criteria

Each subject must not:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;

[1] Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study:

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.*

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents;

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.

7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye;
9) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
11) be a female who is currently pregnant, planning a pregnancy, or lactating.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Any female will be removed from the study should she become pregnant during the course of the study, and she will undergo a pregnancy test at her exit visit for confirmation. The pregnancy test must be confirmed by two (2) additional tests and confirmed by the principal investigator (or sub-investigator if the principal investigator is not present). If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The Investigator will follow-up and document the outcome of the pregnancy and provide a copy of the documentation to the sponsor. The Ora Pregnancy Report Form will be used to report a pregnancy and follow-up.

Reason for withdrawal will be included in the eCRF, and all efforts should be made to schedule the subject for an Exit Visit to complete exit procedures. Any subject who is withdrawn for the study because of an AE will be followed until AE is resolved or as clinically required, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

Sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.5).

6 STUDY PARAMETERS

6.1 Efficacy Measures and Endpoints

6.1.1 Primary Efficacy Endpoint(s)

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3.

6.1.2 Secondary Efficacy Endpoints(s)

The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC at Visit 3:

- Conjunctival redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Ciliary redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)

- Episcleral redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Chemosis evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Eyelid swelling evaluated by the subject (0 to 3 scale, NOT allowing half unit increments)
- Tearing/watery eyes evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)
- Ocular mucous discharge evaluated by the subject CAC (absent/present)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)

6.1.3 Criteria for Effectiveness

This therapeutic equivalence study is designed to evaluate the relative efficacy of EM-100 topical ophthalmic solution compared to vehicle and Zaditor® in the treatment of ocular itching at each designated time point post-CAC at Visit 3 (Day 1, 15-minute onset).

Although this study is being referred to as a "bioequivalence" or "therapeutic equivalence" study, it is in fact a non-inferiority study and all statistical testing will determine whether EM-100 is non-inferior to the reference drug, Zaditor®. Vehicle is included in this study in order to validate the assay.

To demonstrate non-inferiority for ocular itching compared to Zaditor®, EM-100 topical ophthalmic solution needs to show itching scores no worse than 0.75 units (using the same scale) worse than Zaditor® as determined by a one-sided test at alpha = 0.025 for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC.

To demonstrate superiority for ocular itching compared to vehicle, EM-100 topical ophthalmic solution needs to show clinical superiority over vehicle by at least 0.5 units of a 5 point scale for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC, and at least 1 unit for the majority (2:3) of the post-CAC time points. Statistically significant differences at two-sided alpha levels of 0.05 are also required for each post-CAC time point. This statistical significance is expected given the clinical superiority requirements above. Primary and secondary analyses will be tested using a fixed sequence, as described in Section 10.7.

6.2 **Safety Measures**

- Adverse Events (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) at Distance

- Slit Lamp Biomicroscopy

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)

- EM-100 topical ophthalmic solution
- Vehicle of EM-100 topical ophthalmic solution
- Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)

7.1.2 Instructions for Use and Administration

- This trial requires additional attention in order to preserve masking of study treatment. There will be a total of 485 identical appearing kits containing all three treatments labeled A, B, and C. Once the kits arrive at the site, a designated staff member will randomly select 65 kits to be used for the trial. The remaining 420 kits will be identified and stored as retains. Both EM-100 and the vehicle of EM-100 will be identical in appearance as single use vials, while the reference product, Zaditor®, will be in its original bottle. All individual kits will be sealed with tamper evident tape and the sites will be instructed to not open the kits upon receipt of shipment. At no point during the trial (until database lock) will site staff or monitors be allowed to open the kits unless it is the designated "unmasked" technicians. These technicians will ensure that opening of the kits is done in a manner to prevent the other staff and subjects from seeing the investigational product. For each subject treatment will be administered by eye according to a randomization list which will be sent to the site in a sealed envelope and opened at Visit 3 by the unmasked technicians. Following Visit 3 dosing, the technicians will reseal the kits and randomization list envelope using tamper evident tape and return the kits to storage. The sealed randomization list envelope will be filed in the investigator's study file.

- At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100. A randomization list will inform the technicians which corresponding letter treatment should be instilled in the right eye and which one should be instilled in the left eye.

- A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC.

- The pre-specified unmasked technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site. Care will be taken to hide the container (vial or bottle) from the subject. Dosing will occur in a room where no other subjects, staff, or investigators will observe the instillation.

- Investigational product must be stored in a secure area of the clinical site, accessible only to the Investigator(s) or designees at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

- In accordance with 21CFR §320.38 and §320.63, samples of both the test article (EM-100) and reference listed drug (Zaditor®) will be retained and stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel.

7.2 Other Study Supplies

The following supplies will be supplied and/or reconstituted by Ora, Inc.:

- Pregnancy tests (Clarity HCG, RAC Medical Boca Raton, FL).
- The allergens used for skin testing and the conjunctival allergen challenge (cat dander, dog dander, dust mite, cockroach, meadow fescue, rye grass, Bermuda grass, Kentucky bluegrass, Timothy grass, ragweed, white birch, oak, and maple).
- Relief drops (OTC antihistamine/vasoconstrictor combination products).

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 (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board. Failure

to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to return to the clinic for study Visits 1, 2, and 3.

Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

8.1.3 Washout Intervals

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

72 Hours

- contact lenses;

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizers, H_1 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);

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents.

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

8.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion criteria and none of the exclusion criteria prior to Visit 3 to be enrolled in this 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. 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 treatment groups, and to enhance the validity of statistical comparisons.

Once a subject meets qualification criteria at Visit 3 (Day 1), he/she will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.

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

- contact lenses
- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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)
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers
- depot-corticosteroids
- immunosuppressive or cancer chemotherapeutic agents

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

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 the Screening Visit.

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

Currently marketed over-the-counter anti-allergy eye drops (i.e., anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained personnel at the end of Visits 1, 2, and 3 after all evaluations are completed.

8.2.3 Special Diet or Activities

Not Applicable.

8.3 Examination Procedures

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

8.3.1.1 SCREENING VISIT (Day -50 to -22): Screening/ Informed Consent/ Skin Test

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

  Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

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

- *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 45 days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 45 days prior to Visit 1.

- *Review of Inclusion/Exclusion Criteria:* Confirm if subject needs to washout from any current medications and instruct he/she to follow the appropriate washout time periods (refer to Section 8.1.3)

- *Adverse Event Query*

- *Schedule Visit 1:* Qualifying subjects will be scheduled for Visit 1.

8.3.1.2 VISIT 1 (Day -21 ± 3): Titration CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (for females of childbearing potential):* Females of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled.

- *Initial Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify.

- *Initial Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess initial ocular itching and conjunctival redness using the Ora-CAC® scales (see **Appendix 2**). Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score) will be excluded.

- *Initial Slit Lamp Biomicroscopy:* A slit lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions (see **Appendix 2**). Findings of abnormality which are not exclusionary should be recorded as Medical History.

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

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

If the subject fails to react within 10 (±2) minutes, increasingly concentrated doses may be instilled bilaterally at approximately ten-minute intervals until a positive reaction is elicited. If increasing doses are required (i.e., for insufficient bilateral itching and/or redness as evaluated by a trained technician or the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen (up to maximum concentration of 5000 AU), other allergens to which the subject is sensitized may be used starting at the lowest dose.

- *Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Upon completion of the initial titration CAC, subjects will receive an ocular examination by the Investigator to evaluate conjunctival redness and confirm the subject's qualification. Subjects will be asked to assess their ocular itching.

  A positive CAC at Visit 1 is defined as a score of ≥ 2 for redness in the conjunctival vessel bed of each eye and ≥ 2 for itching in each eye within 10 (±2) minutes of receiving that dose of allergen. Any subject who fails to test positively will be excluded from the study.

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

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) by trained study personnel as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 2:* Qualifying subjects will be scheduled to return to the office in one (1) week for Visit 2.

8.3.1.3 VISIT 2 (Day -14 ± 3): Confirmation CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion.

An increase of +0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Pre-CAC Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess pre-CAC ocular itching and conjunctival redness using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score in either eye) will be excluded.

- *Slit Lamp Biomicroscopy*

- *Review of Inclusion/Exclusion Criteria*

- *Confirmation CAC*: For each qualified subject, one drop of the allergen solution, of the same, final dose that elicited a positive reaction at Visit 1, will be administered bilaterally.

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

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 3:* Subjects will be asked to return to the office two (2) weeks later for Visit 3.

8.3.1.4 VISIT 3 (Day 1): Enrollment/Randomization/ In-Office Instillation/ Efficacy CAC/ Study Exit

- *Update of Medical/Medication History*

[1] not necessarily at the same time point

- *Adverse Event Query*

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

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Pre-CAC Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess pre-CAC ocular itching and conjunctival redness using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as >1 redness in conjunctival bed or the presence of any itching in either eye) will be excluded.

- *Slit Lamp Biomicroscopy*

- *Review of Inclusion/Exclusion Criteria*

- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria and qualify to continue in the study will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.

- *Investigational Product Instillation:* A trained study technician will instill one drop of the assigned treatment in the right eye and one drop of the assigned treatment in the left eye, according to the directions for use. The investigational product kit number and the time of instillation will be recorded. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.

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

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

- *Exit Slit Lamp Biomicroscopy*

- *Exit Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Study Exit:* Subjects will be exited from the study.

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

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

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

If a subject is discontinued at a scheduled study visit (i.e. Visit 3), the remaining assessments should be captured on the Unscheduled Visit/ Early Exit Visit pages of the source document and corresponding eCRF. Subjects who screen fail (Screening Visits or Visits 1, 2, or 3) may be scheduled for the Unscheduled Visit at the Investigator's discretion due to follow-up of an ongoing AE.

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 in order 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:

- Assessment of Adverse Events
- Assessment of Concomitant Medications
- Visual Acuity Utilizing an ETDRS chart
- Urine Pregnancy Test (for females of childbearing potential)
- Slit lamp Biomicroscopy

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

8.5 Compliance with Protocol

Subjects who are inappropriately enrolled or no longer fulfill the study eligibility criteria 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 by asking subjects if they changed their dosing regimen since their previous visit. The response will be recorded in the source document and on the eCRF at Visits 1, 2, and 3.

All protocol violations, regardless of causation, will be recorded in the subject's source document as well as eCRF. Major protocol violations will be recorded in the subject's source document, entered in the eCRF, and reported to the IRB, as per the applicable regulations.

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. Subjects who are discontinued from the study will not be replaced.

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 study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.

8.9 Monitoring and Quality Assurance

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

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

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device,

including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

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

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
  - *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the

drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.

- *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE event include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

Adverse events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

  Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

Collection of AEs/SAEs will begin at the time of informed consent.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

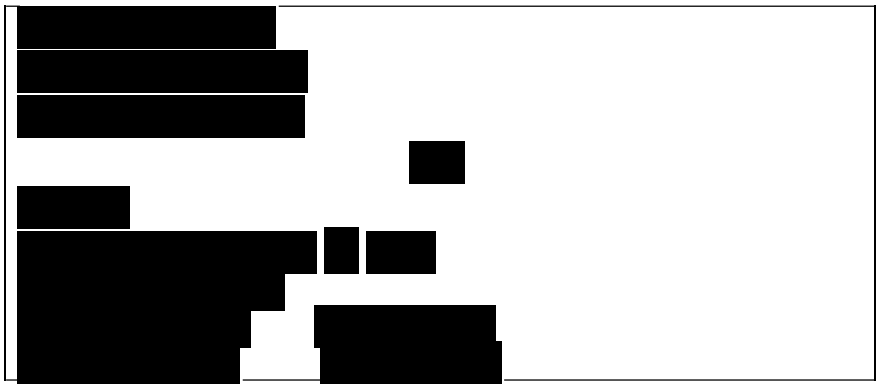
All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate eCRFs. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs. All SAEs, regardless of expectedness or relationship to the IP, will be reported to the FDA as soon as possible but no later than 15 calendar days after becoming aware of the event.

Contact information for reporting SAEs:



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.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

AEs will be followed until:

- Resolution (return to baseline status or to "normal")
- Stabilization of the event has occurred (no improvement or worsening expected by the investigator)
- Event is otherwise explained, regardless of whether the subject is still participating in the study
- Principal investigator determines, for events that do not end (i.e., metastasis), the condition to be chronic. The event can be determined to be resolved or resolved with sequelae.

The Investigator will follow unresolved adverse events to resolution until the subject is lost to follow-up or until the adverse event is otherwise explained. If the subject is lost to follow-up, the Investigator should make three (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 adverse events identified on the last scheduled contact must be recorded on the AE eCRF with the status noted and be followed as aforementioned.

If the Investigator becomes aware of any new information regarding a Serious Adverse Event (i.e., resolution, change in condition, or new treatment), a new Serious Adverse Event/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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Study Populations

10.1.1 Intent-to-Treat Population

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

10.1.2 Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

10.1.3 Safety Population

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

10.2 General Imputation Methods

Missing data is not expected in this single, post-randomization visit study. However, if missing data does result, missing data for the primary efficacy variable will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation techniques on the ITT population. A separate model will be fit for each time point. The model will include variables for treatment, time appropriate baseline measure and response measure.

For sensitivity analysis, the ITT population will also be analyzed using observed data only.

10.3 Statistical Hypotheses

The statistical hypotheses for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® are as follows:

PRIMARY:

H_{01}: Ocular itching scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a1}: Ocular itching scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

SECONDARY:

Conditional upon H_{01} being rejected, the statistical hypothesis for the superiority test between EM-100 ophthalmic solution and vehicle solution will be tested as follows:

H_{02}: There is no difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a2}: There is a difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01} and H_{02} being rejected, the statistical hypothesis for the superiority test between Zaditor® and vehicle solution will be tested as follows:

H_{03}: There is no difference in ocular itching scores between Zaditor® and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a3}: There is a difference in ocular itching scores between Zaditor® and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01}, H_{02}, and H03 being rejected, the statistical hypothesis for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® will be tested as follows:

H_{04}: Conjunctival redness scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a4}: Conjunctival redness scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

10.4 Sample Size

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided

non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.
The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

10.5 Primary Efficacy Analyses

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

As an additional sensitivity analysis, a general linear model will be run with treatment, time point, and time appropriate baseline as covariates for adjustment, accounting for

repeated measurements within each eye as well as the correlation within subjects between eyes. LS Means and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% CIs, will be calculated from this linear model.

The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population using the multiple imputation MCMC method for missing data (if missing data arises) as described in Section 10.2. Sensitivity or supportive analyses will be performed using observed data only for both the ITT and PP populations.

10.6 Secondary Efficacy Analyses

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority test of the primary endpoint. Missing data handling and sensitivity analyses will also follow the methodology used for the primary endpoint. The superiority of EM-100 versus vehicle and of Zaditor® versus vehicle will also be tested as supportive analyses.

Other secondary endpoints (Ciliary redness, Episcleral redness, Chemosis, Eyelid Swelling, Tearing, Ocular Mucous Discharge, Rhinorrhea, Nasal Pruritus, Ear/Palate Pruritus, Nasal Congestion) will also be analyzed as supportive analyses. Other secondary endpoints will be analyzed for the ITT population with observed data only. These secondary endpoints will be analyzed using general linear models for each post-CAC time point (as appropriate) at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models.

10.7 Adjustment for Multiplicity

The primary and secondary analyses will be tested in a fixed sequence to maintain the study-wide Type I error for these analyses. The primary analysis testing non-inferiority of EM-100 versus Zaditor® will be performed first. In order to perform the secondary analysis testing the superiority of EM-100 over vehicle, the primary analysis must first be successful. Conditional upon both the primary analysis and the first secondary analysis being successful, the second secondary analysis comparing Zaditor® and the vehicle of EM-100 will be performed. The fixed sequence testing will proceed as follows:

1) Primary analysis of the primary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for ocular itching at Visit 3
2) Secondary analysis of the primary endpoint: Testing superiority of EM-100 vs. vehicle for ocular itching at Visit 3

3) Secondary analysis of the primary endpoint: Testing superiority of Zaditor® vs. vehicle for ocular itching at Visit 3
4) Analysis of the secondary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for conjunctival redness at Visit 3

In addition, statistical success must be met for all three post-CAC time points for each analysis. Proceeding to the next hierarchical analysis requires all three post-CAC time points are statistically significant for the previous analyses. All other secondary tests will be considered exploratory. Therefore, no other adjustments for multiplicity are required.

10.8 Demographic and Baseline Medical History

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

10.9 Safety Analysis

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

10.10 Interim Analysis

No interim analyses are planned.

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 Harmonization (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 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 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 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 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

Each kit will contain the 3 treatments labeled A, B, and C. The EM-100 and vehicle will consist of five single use 0.4mL vials packaged in an aluminum pouch. Zaditor® will be in its original bottle with the label removed. A label containing the letter A, B, or C will be on the bottles of Zaditor® and the pouches of both EM-100 and vehicle of EM-100. There will be 485 kits created. Kits will be labeled on the outside with a kit number ranging from 001-485. Each kit will be sealed with tamper evident tape.

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. Kits will be left unopened until the authorized unmasked technicians open the assigned kit for administration to each randomized subject. Following administration to the subject, the technicians will return the product to the kit and seal the kit with tamper evident tape.

Investigational product must be stored at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

Upon receiving the shipment of IP, the investigator or his/her designee will select at random the appropriate number of units to be designated as the retain samples. A label will be affixed to the designated units to identify these as "retain samples." These retain samples will not be assigned to study subjects for clinical use. All of the retain samples will be stored in a secure area accessible only to the investigator and his/her designees. The retain samples will be segregated from the investigational product to be assigned to study subjects for clinical use, but will be stored in the same area and under the same conditions for the duration of the study.

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 administered to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP. Note only the kit number and number of kits will be tallied. The kits will remain sealed prior to and following Visit 3. There will be no counting of individual IP inside the kit.

The investigator must also keep an accurate accounting of the retain samples and must properly document the inventory.

11.5.4 Return or Disposal of Investigational Product

All IP used in the clinical trial will be returned to the sponsor (or their designee) or destroyed at the study site. The return or disposal of IP will be specified in writing. All of the retain samples will be shipped to a third party vendor for long-term storage.

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

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

Procedure	Screening Visit	Visit 1	Visit 2	Visit 3
	Day -50 to -22	Day -21 ± 3	Day -14 ± 3	Day 1
Informed Consent/HIPAA[1]	X			
Demographic Data	X			
Medical/Medication History	X			
Medical/Medication History Update		X	X	X
Allergic Skin Test	X			
Visual Acuity		X	X	X
Urine Pregnancy Test (for females of childbearing potential)[2]		X		X
Assessments of Ocular Itching and Conjunctival Redness		X	X	X
Slit Lamp Biomicroscopy		X	X	X
Titration Conjunctival Allergen Challenge		X		
Confirmation Conjunctival Allergen Challenge			X	
Enrollment/Randomization				X
Investigational Product Instillation[3]				X
Efficacy Conjunctival Allergen Challenge				X
Relief Drop Instillation		X	X	X
Adverse Event Query	X	X	X	X
Exit from Study				X

[1] Informed consent must be signed before any study-related procedure can be performed.
[2] 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 surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[3] Instilled 15(+1) minutes prior to CAC

APPENDIX 2: EXAMINATION PROCEDURES, TESTS,

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 only the 'R' charts, and the right eye should be tested first. 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

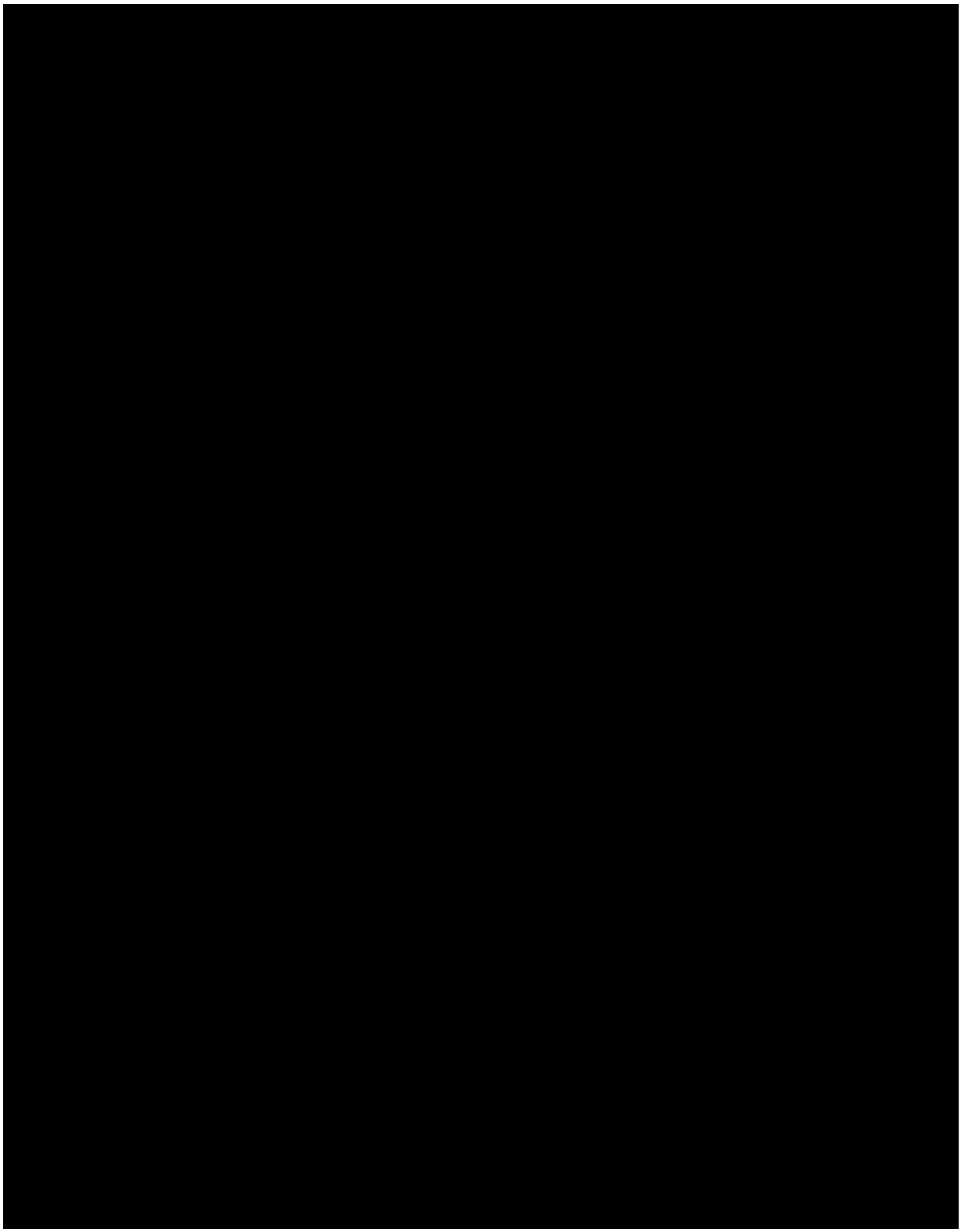
The biomicroscopy and external eye exam will be performed at every visit with the slit lamp at 10x or 16x or equivalent magnification using the investigator's standard slit lamp equipment and procedure. This procedure will be the same for all subjects observed at the investigator's site.

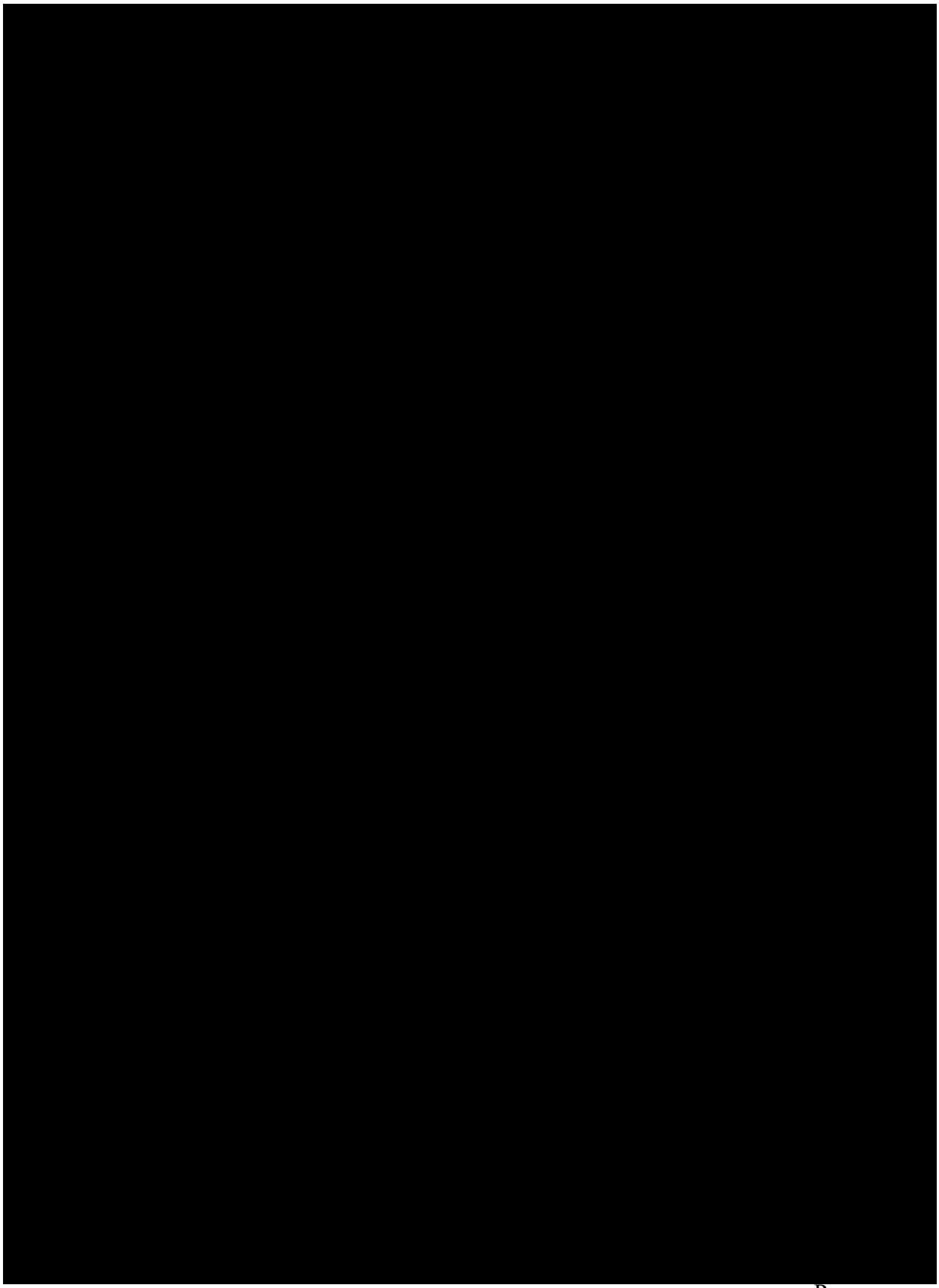
The investigator will determine if findings are within normal limits or if findings indicate an abnormality. Abnormalities should be further described as mild, moderate, or severe.

Observations will be graded as described below.

Lashes	
	0 = Normal
	1 = Abnormal
Eyelid	
Erythema	0 = Normal, no redness
	1 = Abnormal
Edema	0 = Normal, no swelling of the lid tissue
	1 = Abnormal
Conjunctiva	
Erythema	0 = Normal, may appear blanched to reddish-pink without perilimbal injection
	1 = Abnormal
Edema	0 = Normal, no swelling of the conjunctiva
	1 = Abnormal
Papillary Response	0 = Normal, none
	1 = Abnormal
Follicular Response	0 = Normal, none
	1 = Abnormal
Cornea	
Infiltrates	0 = Absent
	1 = Present
Endothelial Changes	0 = Normal, none
	1 = Abnormal, pigment, keratic precipitates, guttata
Edema	0 = Normal None, transparent and clear
	1 = Abnormal
Corneal Neovascularization	0 = Normal, no corneal neovascularization
	1 = Abnormal
Anterior Chamber	
Cells	0 = Normal, No cells seen
	1 = Abnormal (+ to +++ cells)
Flare	0 = Normal, No Tyndall effect
	1 = Abnormal, Tyndall beam in the anterior chamber

Lens Pathology	
	0 = Normal; no opacity in the lens
	1 = Abnormal; existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings.
Scleral Injection	
	0 = Normal, without any redness
	1 = Abnormal





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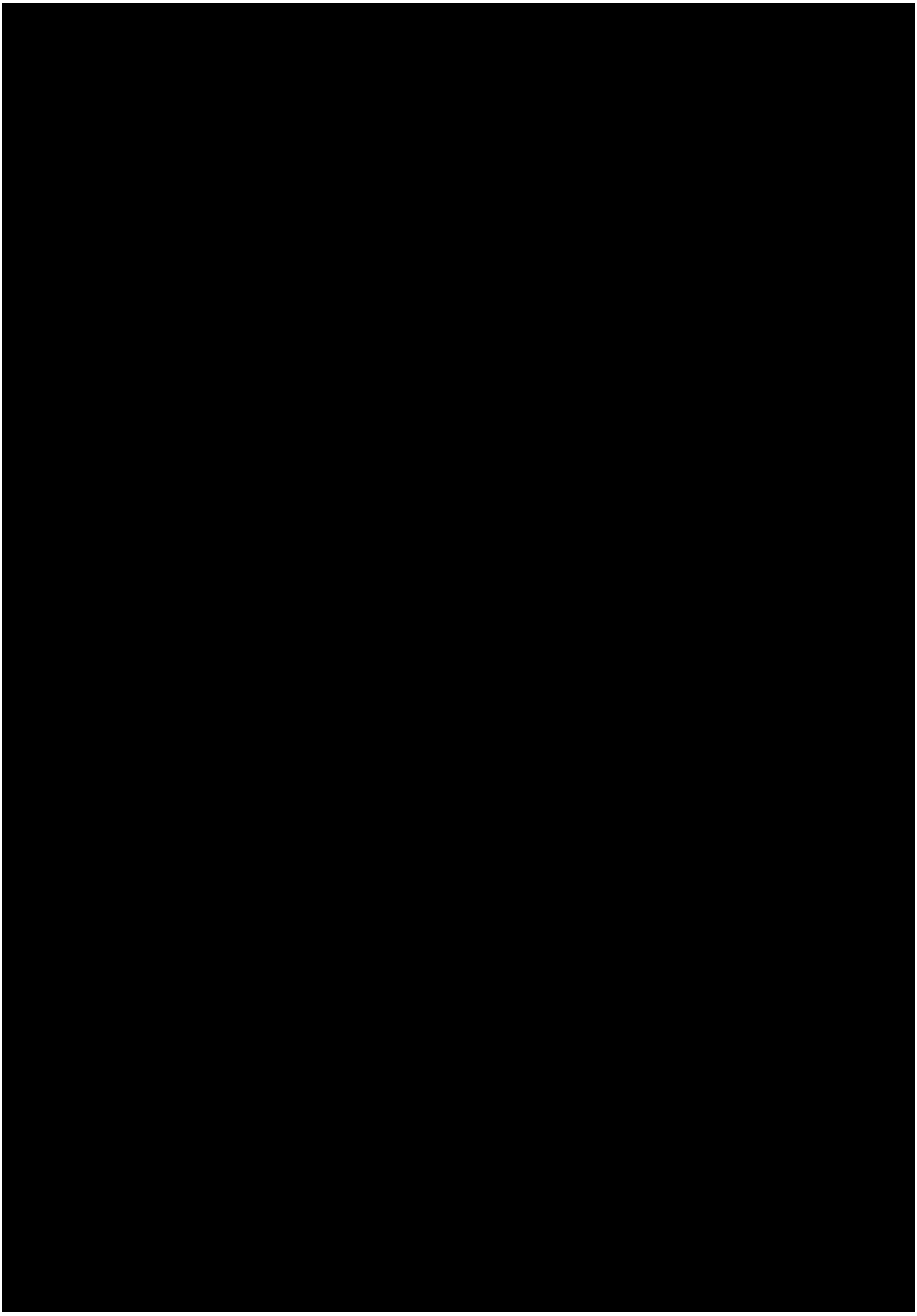


APPENDIX 3: PACKAGE INSERT

Drug Facts

Active ingredients
Ketotifen (0.025%)

(equivalent to ketotifen fumarate 0.035%)

Purpose
Antihistamine

Uses
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

Warnings
For external use only

Do not use
- if solution changes color or becomes cloudy
- if you are sensitive to any ingredient in this product
- to treat contact lens related irritation

When using this product
- do not touch tip of container to any surface to avoid contamination
- remove contact lenses before use
- wait at least 10 minutes before reinserting contact lenses after use
- replace cap after each use

Stop use and ask doctor if you experience any of the following:
- eye pain
- changes in vision
- redness of the eyes
- itching worsens or lasts for more than 72 hours

Keep out of reach of children.

If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- **Adults and children 3 years of age and older:**
  Put 1 drop in the affected eye(s) twice daily, every 8–12 hours, no more than twice per day.
- **Children under 3 years of age:** Consult a doctor.

Other information

- Only for use in the eye.
- Store between 4°–25°C (39°–77°F).

Inactive ingredients

benzalkonium chloride 0.01%, glycerol, purified water, sodium hydroxide, and/or hydrochloric acid

APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT SUMMARY

Section	Page	Description of Change	Rationale
Synopsis, Section 6.1.2. Efficacy Measures and endpoints.	9, 22	Updated Secondary Efficacy Measures and Endpoints: **The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC at Visit 3:** • Conjunctival redness evaluated by the investigator ~~at 7(±1), 15(±1), and 20(±1) minutes post-CAC~~ (0 to 4 scale, allowing half unit increments) • **Ciliary redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)** • **Episcleral redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)** • **Chemosis evaluated by the investigator (0 to 4 scale, allowing half unit increments)** • **Eyelid swelling evaluated by the subject (0 to 3 scale, NOT allowing half unit increments)** • **Tearing/watery eyes evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)** • **Ocular mucous discharge evaluated by the subject CAC (absent/present)** • **Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)**	Additional secondary endpoints added to trial to allow for additional data to be captured.
8.3.1.4 Visit 3 Procedures	33	*Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Assessments of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of ~~conjunctival~~ redness **and chemosis** will be	Additional secondary efficacy measures captured at Visit 3

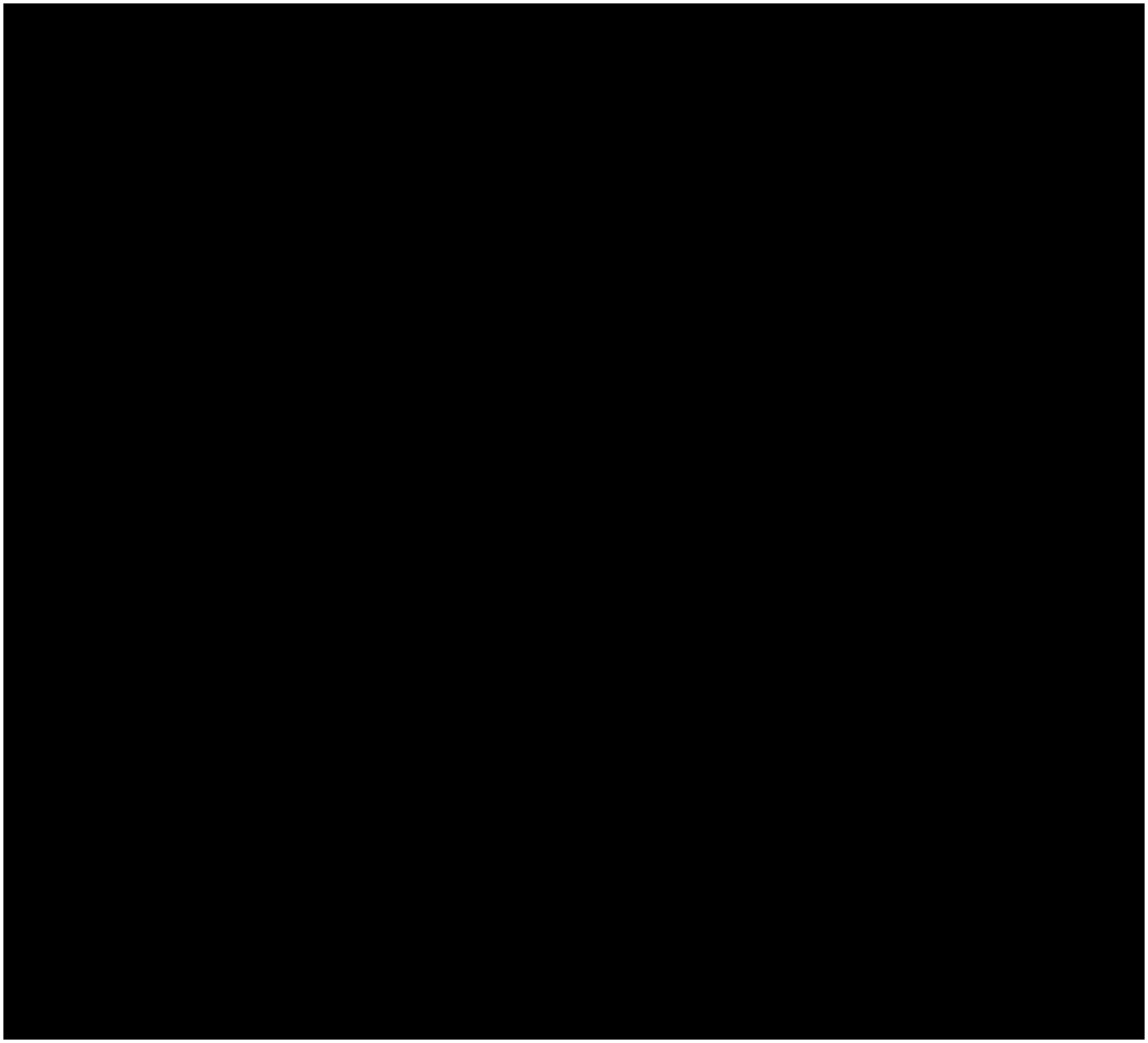
Section	Page	Description of Change	Rationale
		graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge **and assessments of eyelid swelling, tearing/watery eyes, ocular mucous discharge, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge** (Appendix 2).	
10.6 Secondary Efficacy Analyses	44	Secondary endpoints (Ciliary redness , Episcleral redness, Chemosis, Eyelid Swelling, Tearing, Ocular Mucous Discharge, Rhinorrhea, Nasal Pruritus, Ear/Palate Pruritus, Nasal Congestion) will also be analyzed as supportive analyses.	Additional secondary efficacy measures captured at Visit 3
Appendix 2. Slit Lamp Biomicroscopy.	55	Slit Lamp Biomicroscopy scale replaced with a more extensive one.	Allow for a more extensive ocular exam for subject safety
Appendix 2. Allergen Challenge Scales	57	Scales expanded to include the additional secondary efficacy measures of Eyelid swelling, Tearing/Watery Eyes, Ocular Mucous Discharge, Nasal Symptoms, and Chemosis	Scales provided for the additional secondary measures

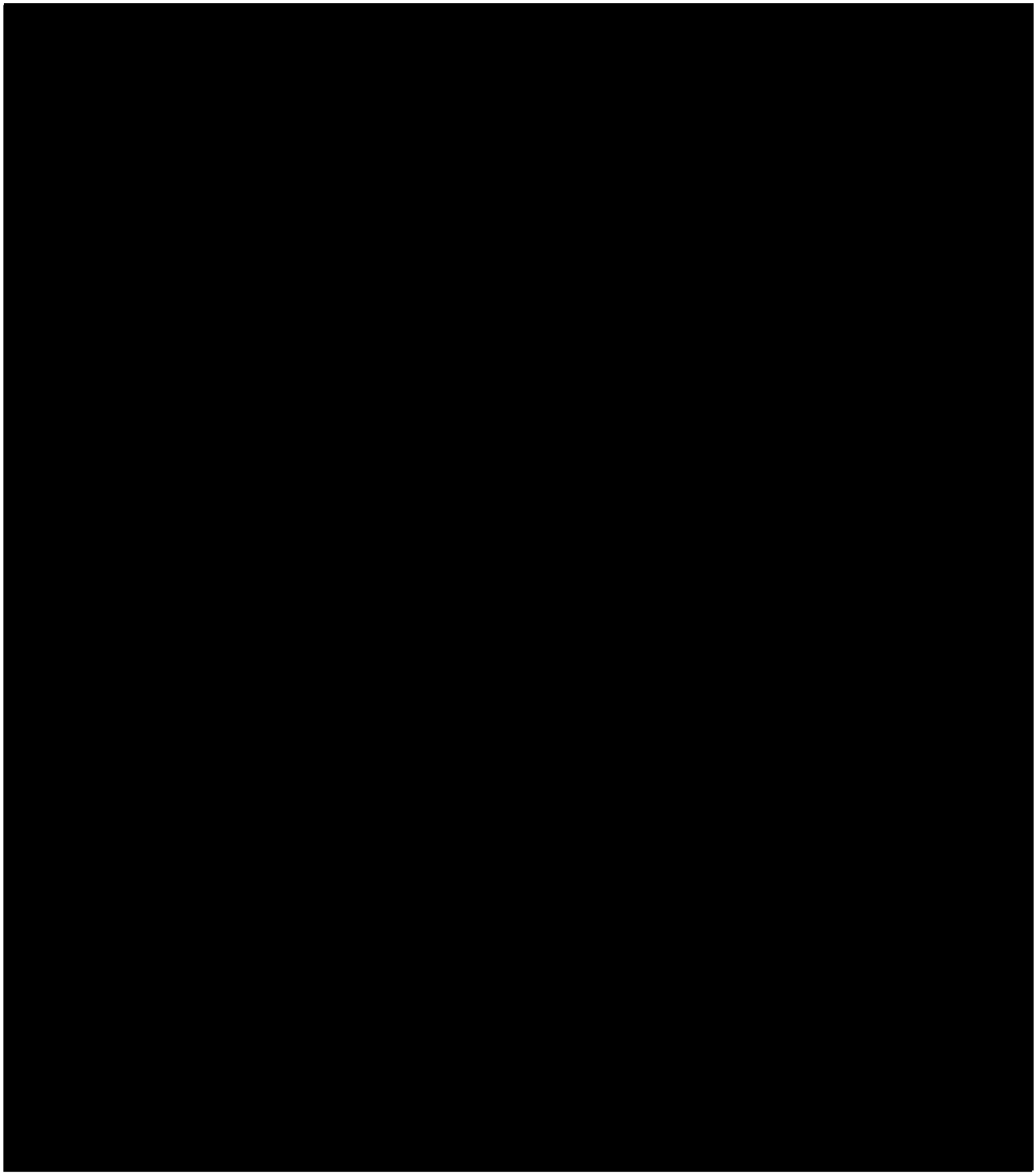
APPENDIX 6: ORA APPROVALS

Protocol Title: A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: 17-100-0011

Final Date: 28 February 2018





APPENDIX 8: INVESTIGATOR'S SIGNATURE

Protocol Title: A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: 17-100-0011

Amendment Date: 28 February 2018

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>
<enter phone number>

Clinical Trial Protocol: 17-100-0011

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Study Phase:	3
Investigational Product Name:	EM-100 topical ophthalmic solution
IND Number:	Not Applicable
Indication:	Allergic Conjunctivitis
Investigators:	Single-center
Sponsor:	EyeMax, LLC 74 Chestnut St. Weston, MA 02493
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:	15 December 2017
Amendment 1:	28 February 2018
Amendment 2:	04 April 2018

Confidentiality Statement

SPONSOR PERSONNEL

President:	[redacted]

ORA PERSONNEL

Medical Monitor:	[redacted]
Chief Medical Officer:	[redacted]
Department Vice President:	[redacted]
Project Lead:	[redacted]

SYNOPSIS

Protocol Title:	A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	17-100-0011
Investigational Product:	EM-100 topical ophthalmic solution
Study Phase:	3
Primary Objective(s):	To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.
Secondary Objective(s):	• To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis. • To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.
Overall Study Design:	
Structure:	*Screening Period:* At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1. *Treatment Period:* At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100 in the right eye and one of the other

	two treatments in the left eye. A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product.
Duration:	This study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.
Controls:	• Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%, EQ 0.025% Base), ANDA 077200 held by Alcon Pharmaceuticals.
Dosage/ Instillation:	At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below: • EM-100 in right eye and Zaditor® in left eye (N ~ 18) • Zaditor® in right eye and EM-100 in left eye (N ~ 18) • EM-100 in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and EM-100 in left eye (N ~ 6) • Zaditor® in right eye and Vehicle in left eye (N ~ 6) • Vehicle in right eye and Zaditor® in left eye (N ~ 6) A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.
Summary of Visit Schedule:	**Screening Visit (Day -50 to -22):** Screening/ Informed Consent/ Skin Test **Visit 1 (Day -21 ± 3):** Titration CAC **Visit 2 (Day -14 ± 3):** Confirmation CAC

	Visit 3 (Day 1): Enrollment/ Randomization/ In-Office Instillation/ Efficacy CAC/ Study 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 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.
Condition/Disease:	Allergic Conjunctivitis
Inclusion Criteria:	*Each subject must:* 1) be at least 18 years of age at the Screening Visit, of either gender and any race; 2) provide written informed consent and sign the HIPAA form; 3) be willing and able to follow all instructions and attend all study visits; 4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months; 5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period; 7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be

	lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart; 9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1; 10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.
Exclusion Criteria:	*Each subject <u>must not</u>:* 1) have known contraindications or sensitivities to the use of the investigational product or any of its components; 2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye); 3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months; 4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

	5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit; 6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study: **7 Days** • systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.* **14 Days** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **45 Days** • depot-corticosteroids; **2 Months** • immunosuppressive or cancer chemotherapeutic agents; *Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.* 7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels

	could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens; 8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye; 9) have planned surgery (ocular or systemic) during the trial period or within 30 days after; 10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial; 11) be a female who is currently pregnant, planning a pregnancy, or lactating.
Study Formulations and Formulation Numbers:	• EM-100 topical ophthalmic solution • Vehicle of EM-100 topical ophthalmic solution • Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)
Evaluation Criteria:	
Efficacy Measures and Endpoints:	**Primary:** • Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. **Secondary:** The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC at Visit 3: • Conjunctival redness evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Ciliary redness evaluated by the investigator (0 to 4

	scale, allowing half unit increments) • Episcleral redness evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Chemosis evaluated by the investigator (0 to 4 scale, allowing half unit increments) • Eyelid swelling evaluated by the subject (0 to 3 scale, NOT allowing half unit increments) • Tearing/watery eyes evaluated by the subject (0 to 4 scale, NOT allowing half unit increments) • Ocular mucous discharge evaluated by the subject CAC (absent/present) • Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)
Safety Measures:	• Adverse Events (reported, elicited, and observed) • Best Corrected Visual Acuity (BCVA) at Distance • Slit Lamp Biomicroscopy

General Statistical Methods and Types of Analyses

The following analysis populations will be defined:

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

Per Protocol Set – The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

Safety Analysis Set – The safety population includes all subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

Sample Size:

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.

The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

Primary Efficacy Analyses:

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes

post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

Secondary Efficacy Analyses:

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority tests of the primary endpoint. Secondary endpoints (Ciliary redness, Episcleral redness, Chemosis, Eyelid Swelling, Tearing, Ocular Mucous Discharge, Rhinorrhea, Nasal Pruritus, Ear/Palate Pruritus, Nasal Congestion) will be analyzed as supportive analyses.

Safety Analyses:

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

Summary of Known and Potential Risks and Benefits to Human Subjects

Known and potential risks of ketotifen fumarate ophthalmic solution (0.035%) include ocular burning/stinging/irritation, headache, rhinorrhea, and photophobia. Benefits include relief and prevention of ocular itching associated with allergic conjunctivitis.

Refer to the Zaditor® Package Insert regarding risks and benefits to human subjects.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
CAC	conjunctival allergen challenge
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DHHS	Department of Health and Human Services
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug application
IP	investigational product
IRB	institutional review board
ITT	intent to treat
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
ND	not done
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PE	polyethylene
PP	per protocol
SAE	serious adverse event
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
VA	visual acuity

1 INTRODUCTION

Allergies affect approximately 15% of the global population and up to 30% of the U.S. population [(1)]. Allergic reactions can vary from a mild, self-limiting condition to a debilitating condition that significantly impairs the quality of life. Allergic conjunctivitis is generally considered a type 1 hypersensitivity reaction, and is the most prevalent allergic condition, representing about a third of all allergic disorders.

The physiologic basis for allergic conjunctivitis is multifactorial and involves both an early acute phase triggered by mast cell degranulation and release of histamine, and a late phase involving various pro-inflammatory mediators [(2)]. Histamine is the primary mediator responsible for the early phase reaction that triggers itching, vasodilation, and vascular leakage leading to ocular redness, chemosis, and blepharitis. The early phase response occurs within minutes to hours following allergen exposure. The itching associated with the early phase allergic reaction has been shown to peak at ~ 5-7 minutes after allergen provocation, which coincides with mast-cell degranulation. Mast cells also synthesize and release cytokines, chemokines, and growth factors that initiate a cascade of inflammatory events leading to a late-phase reaction involving a variety of pro-inflammatory mediators including prostaglandins, leukotrienes, cytokines, and interleukins and characterized by recruitment of eosinophils, neutrophils, and subsequent lymphocytes and macrophages into the conjunctival tissues [(3, 4)].

Ketotifen is a widely effective therapy for the management of ocular allergies. It has demonstrated rapid onset (≤ 15 minutes) and long duration of action (≥ 8 hours) after conjunctival allergen challenge (CAC)[(5, 6)]. Ketotifen fumarate ophthalmic solution 0.035% was found to be safe, well tolerated, and effective for the prevention of the signs and symptoms associated with allergic conjunctivitis in multiple CAC studies[(7-12)]. In an environmental setting, ketotifen fumarate ophthalmic solution 0.035% was found to safely and effectively reduce seasonal allergic conjunctivitis signs and symptoms and prevent recurrence[(13)].

Ketotifen fumarate ophthalmic solution 0.035% (Zaditor®/Zaditen®; Novartis Ophthalmics) is approved in the United States and Canada for the temporary prevention of ocular itching due to allergic conjunctivitis at a dose of one drop in the affected eye twice daily (every 8-12 hours)[(14)]. In 2006, ketotifen fumarate ophthalmic drops 0.035% (ketotifen 0.025%; Alaway®; Bausch and Lomb, Inc., and Zaditor®; Novartis Ophthalmics) were approved by the United States Food and Drug Administration (FDA) for over-the-counter use, with the indication of temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander, at an approved dose of one drop in the affected eye twice daily (every 8-12 hours)[(15)].

EM-100 contains ketotifen ophthalmic solution (0.025%) as a non-preserved formulation in single-dose vials. This is a single-center, randomized, double-masked study to establish the therapeutic equivalence of EM-100 to Zaditor® (ketotifen fumarate

ophthalmic drops 0.035%). EM-100 will need to show non-inferiority to Zaditor® in the treatment of ocular itching following CAC (15 minutes following study medication instillation). The vehicle is included for assay validation.

2 STUDY OBJECTIVES

Primary:

- To demonstrate the non-inferiority of EM-100 to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis.

Secondary:

- To demonstrate that EM-100 is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis.
- To demonstrate that Zaditor® is superior to vehicle in the treatment of ocular itching associated with allergic conjunctivitis
- To demonstrate that EM-100 is non-inferior to Zaditor® in the treatment of conjunctival redness associated with allergic conjunctivitis.

3 CLINICAL HYPOTHESES

The clinical hypotheses are:

- EM-100 is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC 15 minutes following product instillation.
- EM-100 is non-inferior to Zaditor® in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.
- Zaditor® is more effective than vehicle in the treatment of ocular itching associated with allergic conjunctivitis induced by CAC at 15 minutes following product instillation.

4 OVERALL STUDY DESIGN

This is a single-center, randomized, double-masked, contralateral eye study comparing topical EM-100 with Zaditor® and the vehicle of EM-100 in subjects with allergic conjunctivitis. At the Screening Visit, subjects will sign the informed consent form and an allergic skin test will be performed, if required. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-

CAC will undergo the confirmation CAC at Visit 2 using the same allergen they qualified with at Visit 1.

At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or Vehicle in each eye. The treatment arms are listed below:

- EM-100 in right eye and Zaditor® in left eye (N ~ 18)
- Zaditor® in right eye and EM-100 in left eye (N ~ 18)EM-100 in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and EM-100 in left eye (N ~ 6)
- Zaditor® in right eye and Vehicle in left eye (N ~ 6)
- Vehicle in right eye and Zaditor® in left eye (N ~ 6)

A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye (based on randomization). Subjects will undergo CAC approximately 15 minutes post-instillation of the investigational product. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 120 subjects will be screened in order to enroll approximately 60 subjects at a single-center.

5.2 Study Population Characteristics

5.3 Inclusion Criteria

Each subject must:

1) be at least 18 years of age at the Screening Visit, of either gender and any race;
2) provide written informed consent and sign the HIPAA form;
3) be willing and able to follow all instructions and attend all study visits;
4) have a positive history of allergic conjunctivitis for at least 3 months and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at the Screening Visit or within the past 24 months;
5) be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6);

6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 1 and during the study trial period;
7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. 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) have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 1;
10) have a positive bilateral post-CAC reaction (defined as having scores of ≥ 2 ocular itching and ≥ 2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 2.

5.4 Exclusion Criteria

Each subject must not:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;

[1] Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
[2] not necessarily at the same time point

6) use any of the following disallowed medications during the period indicated **prior to Visit 1** and during the study:

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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 1 and will continue to be maintained for the duration of the study.*

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents;

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 1, 2, and 3, after all evaluations are completed.

7) have any significant illness (e.g., any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
8) have a score of >0 for itching and/or >1 for conjunctival redness prior to challenge (at Visits 1, 2, or 3) in either eye;
9) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
10) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
11) be a female who is currently pregnant, planning a pregnancy, or lactating.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Any female will be removed from the study should she become pregnant during the course of the study, and she will undergo a pregnancy test at her exit visit for confirmation. The pregnancy test must be confirmed by two (2) additional tests and confirmed by the principal investigator (or sub-investigator if the principal investigator is not present). If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The Investigator will follow-up and document the outcome of the pregnancy and provide a copy of the documentation to the sponsor. The Ora Pregnancy Report Form will be used to report a pregnancy and follow-up.

Reason for withdrawal will be included in the eCRF, and all efforts should be made to schedule the subject for an Exit Visit to complete exit procedures. Any subject who is withdrawn for the study because of an AE will be followed until AE is resolved or as clinically required, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

Sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.5).

6 STUDY PARAMETERS

6.1 Efficacy Measures and Endpoints

6.1.1 Primary Efficacy Endpoint(s)

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3.

6.1.2 Secondary Efficacy Endpoints(s)

The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC at Visit 3:

- Conjunctival redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Ciliary redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)

- Episcleral redness evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Chemosis evaluated by the investigator (0 to 4 scale, allowing half unit increments)
- Eyelid swelling evaluated by the subject (0 to 3 scale, NOT allowing half unit increments)
- Tearing/watery eyes evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)
- Ocular mucous discharge evaluated by the subject CAC (absent/present)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0 to 4 scale, NOT allowing half unit increments)

6.1.3 Criteria for Effectiveness

This therapeutic equivalence study is designed to evaluate the relative efficacy of EM-100 topical ophthalmic solution compared to vehicle and Zaditor® in the treatment of ocular itching at each designated time point post-CAC at Visit 3 (Day 1, 15-minute onset).

Although this study is being referred to as a "bioequivalence" or "therapeutic equivalence" study, it is in fact a non-inferiority study and all statistical testing will determine whether EM-100 is non-inferior to the reference drug, Zaditor®. Vehicle is included in this study in order to validate the assay.

To demonstrate non-inferiority for ocular itching compared to Zaditor®, EM-100 topical ophthalmic solution needs to show itching scores no worse than 0.75 units (using the same scale) worse than Zaditor® as determined by a one-sided test at alpha = 0.025 for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC.

To demonstrate superiority for ocular itching compared to vehicle, EM-100 topical ophthalmic solution needs to show clinical superiority over vehicle by at least 0.5 units of a 5 point scale for all 3 post-CAC time points, 3(±1), 5(±1), and 7(±1) minutes post-CAC, and at least 1 unit for the majority (2:3) of the post-CAC time points. Statistically significant differences at two-sided alpha levels of 0.05 are also required for each post-CAC time point. This statistical significance is expected given the clinical superiority requirements above. Primary and secondary analyses will be tested using a fixed sequence, as described in Section 10.7.

6.2 **Safety Measures**

- Adverse Events (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) at Distance

- Slit Lamp Biomicroscopy

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment(s)/ Formulation(s)

- EM-100 topical ophthalmic solution
- Vehicle of EM-100 topical ophthalmic solution
- Zaditor® (ketotifen fumarate ophthalmic solution 0.035%)

7.1.2 Instructions for Use and Administration

- This trial requires additional attention in order to preserve masking of study treatment. There will be a total of 485 identical appearing kits containing all three treatments labeled A, B, and C. Once the kits arrive at the site, a designated staff member will randomly select 65 kits to be used for the trial. The remaining 420 kits will be identified and stored as retains. Both EM-100 and the vehicle of EM-100 will be identical in appearance as single use vials, while the reference product, Zaditor®, will be in its original bottle. All individual kits will be sealed with tamper evident tape and the sites will be instructed to not open the kits upon receipt of shipment. At no point during the trial (until database lock) will site staff or monitors be allowed to open the kits unless it is the designated "unmasked" technicians. These technicians will ensure that opening of the kits is done in a manner to prevent the other staff and subjects from seeing the investigational product. For each subject treatment will be administered by eye according to a randomization list which will be sent to the site in a sealed envelope and opened at Visit 3 by the unmasked technicians. Following Visit 3 dosing, the technicians will reseal the kits and randomization list envelope using tamper evident tape and return the kits to storage. The sealed randomization list envelope will be filed in the investigator's study file.

- At Visit 3, qualifying subjects will be enrolled and randomized to receive EM-100, Zaditor®, or vehicle of EM-100. A randomization list will inform the technicians which corresponding letter treatment should be instilled in the right eye and which one should be instilled in the left eye.

- A trained study technician will instill one (1) drop of the assigned treatment in the right eye and one (1) drop of the assigned treatment in the left eye approximately 15(+1) minutes prior to CAC.

- The pre-specified unmasked technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site. Care will be taken to hide the container (vial or bottle) from the subject. Dosing will occur in a room where no other subjects, staff, or investigators will observe the instillation.

- Investigational product must be stored in a secure area of the clinical site, accessible only to the Investigator(s) or designees at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

- In accordance with 21CFR §320.38 and §320.63, samples of both the test article (EM-100) and reference listed drug (Zaditor®) will be retained and stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel.

7.2 Other Study Supplies

The following supplies will be supplied and/or reconstituted by Ora, Inc.:

- Pregnancy tests (Clarity HCG, RAC Medical Boca Raton, FL).
- The allergens used for skin testing and the conjunctival allergen challenge (cat dander, dog dander, dust mite, cockroach, meadow fescue, rye grass, Bermuda grass, Kentucky bluegrass, Timothy grass, ragweed, white birch, oak, and maple).
- Relief drops (OTC antihistamine/vasoconstrictor combination products).

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 (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board. Failure

to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to return to the clinic for study Visits 1, 2, and 3.

Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

8.1.3 Washout Intervals

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

72 Hours

- contact lenses;

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizers, H_1 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);

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents.

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

8.1.4 Procedures for Final Study Entry

Subjects must meet all of the inclusion criteria and none of the exclusion criteria prior to Visit 3 to be enrolled in this 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. 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 treatment groups, and to enhance the validity of statistical comparisons.

Once a subject meets qualification criteria at Visit 3 (Day 1), he/she will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.

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

- contact lenses
- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 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)
- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers
- depot-corticosteroids
- immunosuppressive or cancer chemotherapeutic agents

Note: Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.

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 the Screening Visit.

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

Currently marketed over-the-counter anti-allergy eye drops (i.e., anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained personnel at the end of Visits 1, 2, and 3 after all evaluations are completed.

8.2.3 Special Diet or Activities

Not Applicable.

8.3 Examination Procedures

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

8.3.1.1 SCREENING VISIT (Day -50 to -22): Screening/ Informed Consent/ Skin Test

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

  Prior to the completion of the screening visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects can be re-screened a maximum of two times.

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

- *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 45 days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 45 days prior to Visit 1.

- *Review of Inclusion/Exclusion Criteria:* Confirm if subject needs to washout from any current medications and instruct he/she to follow the appropriate washout time periods (refer to Section 8.1.3)

- *Adverse Event Query*

- *Schedule Visit 1:* Qualifying subjects will be scheduled for Visit 1.

8.3.1.2 VISIT 1 (Day -21 ± 3): Titration CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Urine Pregnancy Test (for females of childbearing potential):* Females of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled.

- *Initial Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify.

- *Initial Ocular Itching and Conjunctival Redness Assessments:* The investigator and the subject will assess initial ocular itching and conjunctival redness using the Ora-CAC® scales (see **Appendix 2**). Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score) will be excluded.

- *Initial Slit Lamp Biomicroscopy:* A slit lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions (see **Appendix 2**). Findings of abnormality which are not exclusionary should be recorded as Medical History.

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

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

If the subject fails to react within 10 (±2) minutes, increasingly concentrated doses may be instilled bilaterally at approximately ten-minute intervals until a positive reaction is elicited. If increasing doses are required (i.e., for insufficient bilateral itching and/or redness as evaluated by a trained technician or the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen (up to maximum concentration of 5000 AU), other allergens to which the subject is sensitized may be used starting at the lowest dose.

- *Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Upon completion of the initial titration CAC, subjects will receive an ocular examination by the Investigator to evaluate conjunctival redness and confirm the subject's qualification. Subjects will be asked to assess their ocular itching.

  A positive CAC at Visit 1 is defined as a score of ≥ 2 for redness in the conjunctival vessel bed of each eye and ≥ 2 for itching in each eye within 10 (±2) minutes of receiving that dose of allergen. Any subject who fails to test positively will be excluded from the study.

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

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) by trained study personnel as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 2:* Qualifying subjects will be scheduled to return to the office in one (1) week for Visit 2.

8.3.1.3 VISIT 2 (Day -14 ± 3): Confirmation CAC

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion.

An increase of +0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

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

- *Slit Lamp Biomicroscopy*

- *Review of Inclusion/Exclusion Criteria*

- *Confirmation CAC*: For each qualified subject, one drop of the allergen solution, of the same, final dose that elicited a positive reaction at Visit 1, will be administered bilaterally.

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

- *Review of Inclusion/Exclusion Criteria*

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Schedule Visit 3:* Subjects will be asked to return to the office two (2) weeks later for Visit 3.

[1] not necessarily at the same time point

8.3.1.4 VISIT 3 (Day 1): Enrollment/Randomization/ In-Office Instillation/ Efficacy CAC/ Study Exit

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Urine Pregnancy Test (for females of childbearing potential)*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessments:* The investigator and the subject will assess pre-CAC ocular and nasal allergic signs and symptoms using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as >1 redness in conjunctival bed or the presence of any itching in either eye) will be excluded.
- *Slit Lamp Biomicroscopy*
- *Review of Inclusion/Exclusion Criteria*
- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria and qualify to continue in the study will be enrolled and randomized to receive EM-100, Zaditor®, or the vehicle of EM-100. A separate treatment will be assigned to each eye. Subjects will be assigned the lowest four (4) digit randomization number available.
- *Investigational Product Instillation:* A trained study technician will instill one drop of the assigned treatment in the right eye and one drop of the assigned treatment in the left eye, according to the directions for use. The investigational product kit number and the time of instillation will be recorded. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other study procedures at the site.
- *Efficacy CAC*: Each subject will receive one drop of the allergen solution of the same, final dose that elicited a positive reaction at Visit 1 bilaterally, 15(+1) minutes post-instillation of investigational product.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessments:* Assessments of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the

Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge and assessments of eyelid swelling, tearing/watery eyes, ocular mucous discharge, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**).

- *Exit Slit Lamp Biomicroscopy*

- *Exit Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease from Visit 1 may be documented as an AE per the investigator's discretion. An increase of 0.22 or more should be brought to the attention of the investigator. Visual Acuity may be repeated in instances of significant decreases.

- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.

- *Adverse Event Query*

- *Study Exit:* Subjects will be exited from the study.

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

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

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

If a subject is discontinued at a scheduled study visit (i.e. Visit 3), the remaining assessments should be captured on the Unscheduled Visit/ Early Exit Visit pages of the source document and corresponding eCRF. Subjects who screen fail (Screening Visits or Visits 1, 2, or 3) may be scheduled for the Unscheduled Visit at the Investigator's discretion due to follow-up of an ongoing AE.

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 in order 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:

- Assessment of Adverse Events
- Assessment of Concomitant Medications
- Visual Acuity Utilizing an ETDRS chart
- Urine Pregnancy Test (for females of childbearing potential)
- Slit lamp Biomicroscopy

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

8.5 Compliance with Protocol

Subjects who are inappropriately enrolled or no longer fulfill the study eligibility criteria 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 by asking subjects if they changed their dosing regimen since their previous visit. The response will be recorded in the source document and on the eCRF at Visits 1, 2, and 3.

All protocol violations, regardless of causation, will be recorded in the subject's source document as well as eCRF. Major protocol violations will be recorded in the subject's source document, entered in the eCRF, and reported to the IRB, as per the applicable regulations.

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. Subjects who are discontinued from the study will not be replaced.

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 study consists of four (4) office visits (Screening Visit, Visit 1, Visit 2, and Visit 3) over a period of approximately three to five (3-5) weeks.

8.9 Monitoring and Quality Assurance

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

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

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise

from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

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

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug

class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.

- *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE event include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

Adverse events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect.

  Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

Collection of AEs/SAEs will begin at the time of informed consent.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate eCRFs. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs. All SAEs, regardless of expectedness or relationship to the IP, will be reported to the FDA as soon as possible but no later than 15 calendar days after becoming aware of the event.

Contact information for reporting SAEs:

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.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

AEs will be followed until:

- Resolution (return to baseline status or to "normal")
- Stabilization of the event has occurred (no improvement or worsening expected by the investigator)
- Event is otherwise explained, regardless of whether the subject is still participating in the study
- Principal investigator determines, for events that do not end (i.e., metastasis), the condition to be chronic. The event can be determined to be resolved or resolved with sequelae.

The Investigator will follow unresolved adverse events to resolution until the subject is lost to follow-up or until the adverse event is otherwise explained. If the subject is lost to follow-up, the Investigator should make three (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 adverse events identified on the last scheduled contact must be recorded on the AE eCRF with the status noted and be followed as aforementioned.

If the Investigator becomes aware of any new information regarding a Serious Adverse Event (i.e., resolution, change in condition, or new treatment), a new Serious Adverse Event/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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Study Populations

10.1.1 Intent-to-Treat Population

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

10.1.2 Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 3 (Day 1) with no major protocol

deviations. This population will be analyzed as treated using observed data only for confirmatory analyses. Major protocol deviations will be determined prior to unmasking any subject data.

10.1.3 Safety Population

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

10.2 General Imputation Methods

Missing data is not expected in this single, post-randomization visit study. However, if missing data does result, missing data for the primary efficacy variable will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation techniques on the ITT population. A separate model will be fit for each time point. The model will include variables for treatment, time appropriate baseline measure and response measure.

For sensitivity analysis, the ITT population will also be analyzed using observed data only.

10.3 Statistical Hypotheses

The statistical hypotheses for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® are as follows:

PRIMARY:

H_{01}: Ocular itching scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a1}: Ocular itching scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

SECONDARY:

Conditional upon H_{01} being rejected, the statistical hypothesis for the superiority test between EM-100 ophthalmic solution and vehicle solution will be tested as follows:

H_{02}: There is no difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a2}: There is a difference in ocular itching scores between EM-100 topical ophthalmic solution and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01} and H_{02} being rejected, the statistical hypothesis for the superiority test between Zaditor® and vehicle solution will be tested as follows:

H_{03}: There is no difference in ocular itching scores between Zaditor® and vehicle treated subjects for at least one of the three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a3}: There is a difference in ocular itching scores between Zaditor® and vehicle treated subjects for all three primary time points (3[±1], 5[±1], and 7[±1] minutes post-CAC) at Visit 3 (Day 1).

Conditional upon H_{01}, H_{02}, and H03 being rejected, the statistical hypothesis for the non-inferiority test between EM-100 ophthalmic solution and Zaditor® will be tested as follows:

H_{04}: Conjunctival redness scores are more than 0.75 units worse for EM-100 topical ophthalmic solution than Zaditor® treated subjects for at least one of the three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

H_{a4}: Conjunctival redness scores are no more than 0.75 units higher for EM-100 topical ophthalmic solution than Zaditor® treated subjects for all three primary time points (7[±1], 15[±1], and 20[±1] minutes post-CAC) at Visit 3 (Day 1).

10.4 Sample Size

The following treatment combinations will be randomized. The eye receiving each test article will also be randomized:

- 18 subjects with EM-100 in right eye and Zaditor® in left eye
- 18 subjects with Zaditor® in right eye and EM-100 in left eye
- 6 subjects with EM-100 in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and EM-100 in left eye
- 6 subjects with Zaditor® in right eye and Vehicle in left eye
- 6 subjects with Vehicle in right eye and Zaditor® in left eye

This sample size requires a total of 60 randomized subjects, while providing 48 eyes treated with each of EM-100 and Zaditor® and 24 eyes treated with vehicle, for a 2:2:1 ratio of treatments across all treated eyes.

This sample size will provide >99% power to show that EM-100 treated eyes are non-inferior to Zaditor® treated eyes at each time point with respect to ocular itching. The power calculation assumes no treatment difference between EM-100 and Zaditor®, a common standard deviation of 1.0 unit, a non-inferiority limit of 0.75, and a one-sided non-inferiority test at alpha=0.025. The power becomes >97% when considering that non-inferiority is required for all 3 CAC time points, assuming independence between time points.

This sample size will also provide >97% power to show that EM-100 treated eyes have better itching scores than the vehicle treated eyes at each time point. The power calculation assumes a treatment difference of 1.0 units, a common standard deviation of 1.0 unit, and a two-sided test at alpha=0.05. The power becomes >91% when considering that statistical significance is required for all 3 CAC time points.
The test of non-inferiority between EM-100 and Zaditor® must meet statistical significance as the primary analysis. Upon showing non-inferiority for the primary analysis, the test of superiority between EM-100 and vehicle will be performed. The overall study power for the primary analysis and first secondary analysis is expected to be >88%.

Additionally, this sample size yields >91% probability of showing a point estimate difference for itching of at least 1.0 unit between EM-100 and vehicle for a majority of the post-CAC® time points and 0.5 units for all of the post-CAC time points. This assumes a common standard deviation of 1.0 unit, a difference in the study between EM-100 and vehicle of at least 1.2 units at the 3(±1), 5(±1), and 7(±1) minutes post-CAC time points for ocular itching, and independence between time points. In the power calculations, a conservative treatment difference of 1.0 unit was assumed to show a worst-case scenario; however, a treatment difference of 1.2 units is plausible and is expected to show clinical significance with high likelihood, and is therefore used in this probability calculation.

10.5 **Primary Efficacy Analyses**

The primary efficacy endpoint is ocular itching assessed at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visit 3. The primary analysis is a non-inferiority test of EM-100 versus Zaditor®. Ocular itching will be analyzed using a general linear model for each post-CAC time point at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models. For the primary analysis, or the non-inferiority test of EM-100 versus Zaditor® (H_{01}), the one-sided assessment will be made by looking at the upper limit of the two-sided 95% CI. For the superiority tests at each post-CAC time point (H_{02} and H_{03}), treatment differences will

be considered statistically significant if they are significant at a two-sided significance level of $\alpha = 0.05$.

As an additional sensitivity analysis, a general linear model will be run with treatment, time point, and time appropriate baseline as covariates for adjustment, accounting for repeated measurements within each eye as well as the correlation within subjects between eyes. LS Means and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% CIs, will be calculated from this linear model.

The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population using the multiple imputation MCMC method for missing data (if missing data arises) as described in Section 10.2. Sensitivity or supportive analyses will be performed using observed data only for both the ITT and PP populations.

10.6 Secondary Efficacy Analyses

Analyses will be performed on the secondary endpoint of conjunctival redness in a manner similar to the non-inferiority test of the primary endpoint. Missing data handling and sensitivity analyses will also follow the methodology used for the primary endpoint. The superiority of EM-100 versus vehicle and of Zaditor® versus vehicle will also be tested as supportive analyses.

Other secondary endpoints (Ciliary redness, Episcleral redness, Chemosis, Eyelid Swelling, Tearing, Ocular Mucous Discharge, Rhinorrhea, Nasal Pruritus, Ear/Palate Pruritus, Nasal Congestion) will also be analyzed as supportive analyses. Other secondary endpoints will be analyzed for the ITT population with observed data only. These secondary endpoints will be analyzed using general linear models for each post-CAC time point (as appropriate) at Visit 3, with the time appropriate post-CAC score at baseline (Visit 2) as a covariate and accounting for the correlation within subjects, between eyes. Least Square Means (LS Means) and the estimated treatment differences (EM-100 – comparator) with the corresponding 95% confidence intervals (CIs), will be calculated from these linear models.

10.7 Adjustment for Multiplicity

The primary and secondary analyses will be tested in a fixed sequence to maintain the study-wide Type I error for these analyses. The primary analysis testing non-inferiority of EM-100 versus Zaditor® will be performed first. In order to perform the secondary analysis testing the superiority of EM-100 over vehicle, the primary analysis must first be successful. Conditional upon both the primary analysis and the first secondary analysis being successful, the second secondary analysis comparing Zaditor® and the vehicle of EM-100 will be performed. The fixed sequence testing will proceed as follows:

1) Primary analysis of the primary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for ocular itching at Visit 3
2) Secondary analysis of the primary endpoint: Testing superiority of EM-100 vs. vehicle for ocular itching at Visit 3
3) Secondary analysis of the primary endpoint: Testing superiority of Zaditor® vs. vehicle for ocular itching at Visit 3
4) Analysis of the secondary endpoint: Testing non-inferiority of EM-100 vs. Zaditor® for conjunctival redness at Visit 3

In addition, statistical success must be met for all three post-CAC time points for each analysis. Proceeding to the next hierarchical analysis requires all three post-CAC time points are statistically significant for the previous analyses. All other secondary tests will be considered exploratory. Therefore, no other adjustments for multiplicity are required.

10.8 Demographic and Baseline Medical History

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

10.9 Safety Analysis

Safety will be assessed by evaluating the incidence of subjects with any adverse events during the entire study. The percentage of subjects with any AEs will be summarized, as well as the percentage of subjects with any treatment-emergent adverse events (TEAEs), summarized for each treatment combination. Ocular TEAEs will similarly be summarized by eye for each treatment group. Incidence will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Adverse events will also be summarized for treatment-related TEAEs, SAEs, by maximal severity, and by day of onset relative to the start of treatment.

The additional safety variables of slit lamp biomicroscopy and visual acuity will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. In all cases, outcomes will be summarized by eye for each treatment group. Changes and shifts from baseline will also be summarized where applicable.

10.10 Interim Analysis

No interim analyses are planned.

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 Harmonization (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 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 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 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 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

Each kit will contain the 3 treatments labeled A, B, and C. The EM-100 and vehicle will consist of five single use 0.4mL vials packaged in an aluminum pouch. Zaditor® will be in its original bottle with the label removed. A label containing the letter A, B, or C will be on the bottles of Zaditor® and the pouches of both EM-100 and vehicle of EM-100. There will be 485 kits created. Kits will be labeled on the outside with a kit number ranging from 001-485. Each kit will be sealed with tamper evident tape.

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. Kits will be left unopened until the authorized unmasked technicians open the assigned kit for administration to each randomized subject. Following administration to the subject, the technicians will return the product to the kit and seal the kit with tamper evident tape.

Investigational product must be stored at room temperature between 20-25°C (68-77°F). All investigational product will be returned to inventory after use.

Upon receiving the shipment of IP, the investigator or his/her designee will select at random the appropriate number of units to be designated as the retain samples. A label will be affixed to the designated units to identify these as "retain samples." These retain samples will not be assigned to study subjects for clinical use. All of the retain samples will be stored in a secure area accessible only to the investigator and his/her designees. The retain samples will be segregated from the investigational product to be assigned to study subjects for clinical use, but will be stored in the same area and under the same conditions for the duration of the study.

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 administered to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP. Note only the kit number and number of kits will be tallied. The kits will remain sealed prior to and following Visit 3. There will be no counting of individual IP inside the kit.

The investigator must also keep an accurate accounting of the retain samples and must properly document the inventory.

11.5.4 Return or Disposal of Investigational Product

All IP used in the clinical trial will be returned to the sponsor (or their designee) or destroyed at the study site. The return or disposal of IP will be specified in writing. All of the retain samples will be shipped to a third party vendor for long-term storage.

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

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

Procedure	Screening Visit	Visit 1	Visit 2	Visit 3
	Day -50 to -22	Day -21 ± 3	Day -14 ± 3	Day 1
Informed Consent/HIPAA[1]	X			
Demographic Data	X			
Medical/Medication History	X			
Medical/Medication History Update		X	X	X
Allergic Skin Test	X			
Visual Acuity		X	X	X
Urine Pregnancy Test (for females of childbearing potential)[2]		X		X
Assessments of Ocular Itching and Conjunctival Redness		X	X	X
Slit Lamp Biomicroscopy		X	X	X
Titration Conjunctival Allergen Challenge		X		
Confirmation Conjunctival Allergen Challenge			X	
Enrollment/Randomization				X
Investigational Product Instillation[3]				X
Efficacy Conjunctival Allergen Challenge				X
Relief Drop Instillation		X	X	X
Adverse Event Query	X	X	X	X
Exit from Study				X

[1] Informed consent must be signed before any study-related procedure can be performed.
[2] 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 surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[3] Instilled 15(+1) minutes prior to CAC

APPENDIX 2: EXAMINATION PROCEDURES, TESTS,

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 only the 'R' charts, and the right eye should be tested first. 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

The biomicroscopy and external eye exam will be performed at every visit with the slit lamp at 10x or 16x or equivalent magnification using the investigator's standard slit lamp equipment and procedure. This procedure will be the same for all subjects observed at the investigator's site.

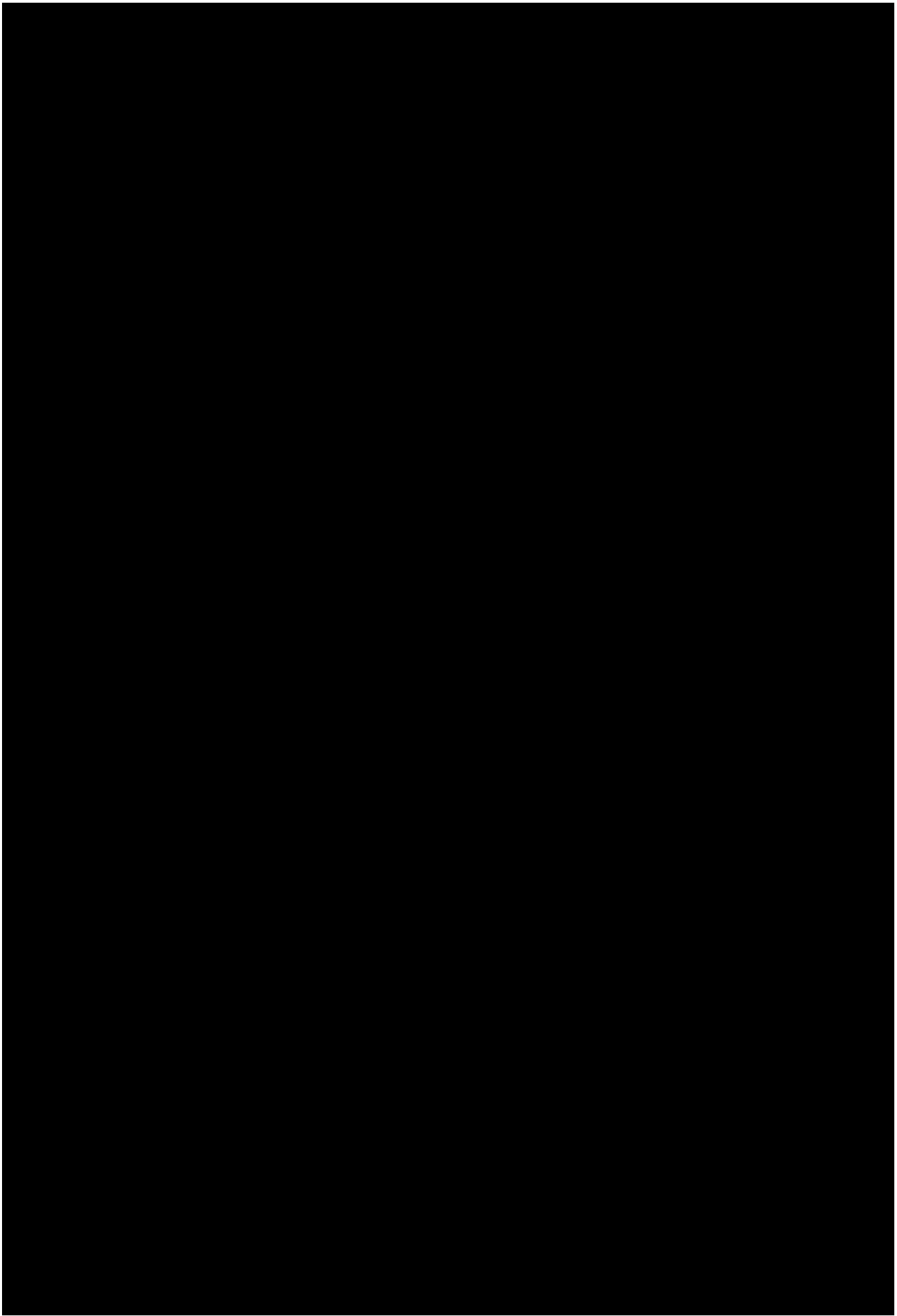
The investigator will determine if findings are within normal limits or if findings indicate an abnormality. Abnormalities should be further described as mild, moderate, or severe.

Observations will be graded as described below.

Lashes	
	0 = Normal
	1 = Abnormal
Eyelid	
Erythema	0 = Normal, no redness
	1 = Abnormal
Edema	0 = Normal, no swelling of the lid tissue
	1 = Abnormal
Conjunctiva	
Erythema	0 = Normal, may appear blanched to reddish-pink without perilimbal injection
	1 = Abnormal
Edema	0 = Normal, no swelling of the conjunctiva
	1 = Abnormal
Papillary Response	0 = Normal, none
	1 = Abnormal
Follicular Response	0 = Normal, none
	1 = Abnormal
Cornea	
Infiltrates	0 = Absent
	1 = Present
Endothelial Changes	0 = Normal, none
	1 = Abnormal, pigment, keratic precipitates, guttata
Edema	0 = Normal None, transparent and clear
	1 = Abnormal
Corneal Neovascularization	0 = Normal, no corneal neovascularization
	1 = Abnormal
Anterior Chamber	
Cells	0 = Normal, No cells seen
	1 = Abnormal (+ to +++ cells)
Flare	0 = Normal, No Tyndall effect
	1 = Abnormal, Tyndall beam in the anterior chamber

Lens Pathology	
	0 = Normal; no opacity in the lens
	1 = Abnormal; existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings.
Scleral Injection	
	0 = Normal, without any redness
	1 = Abnormal

[redacted]



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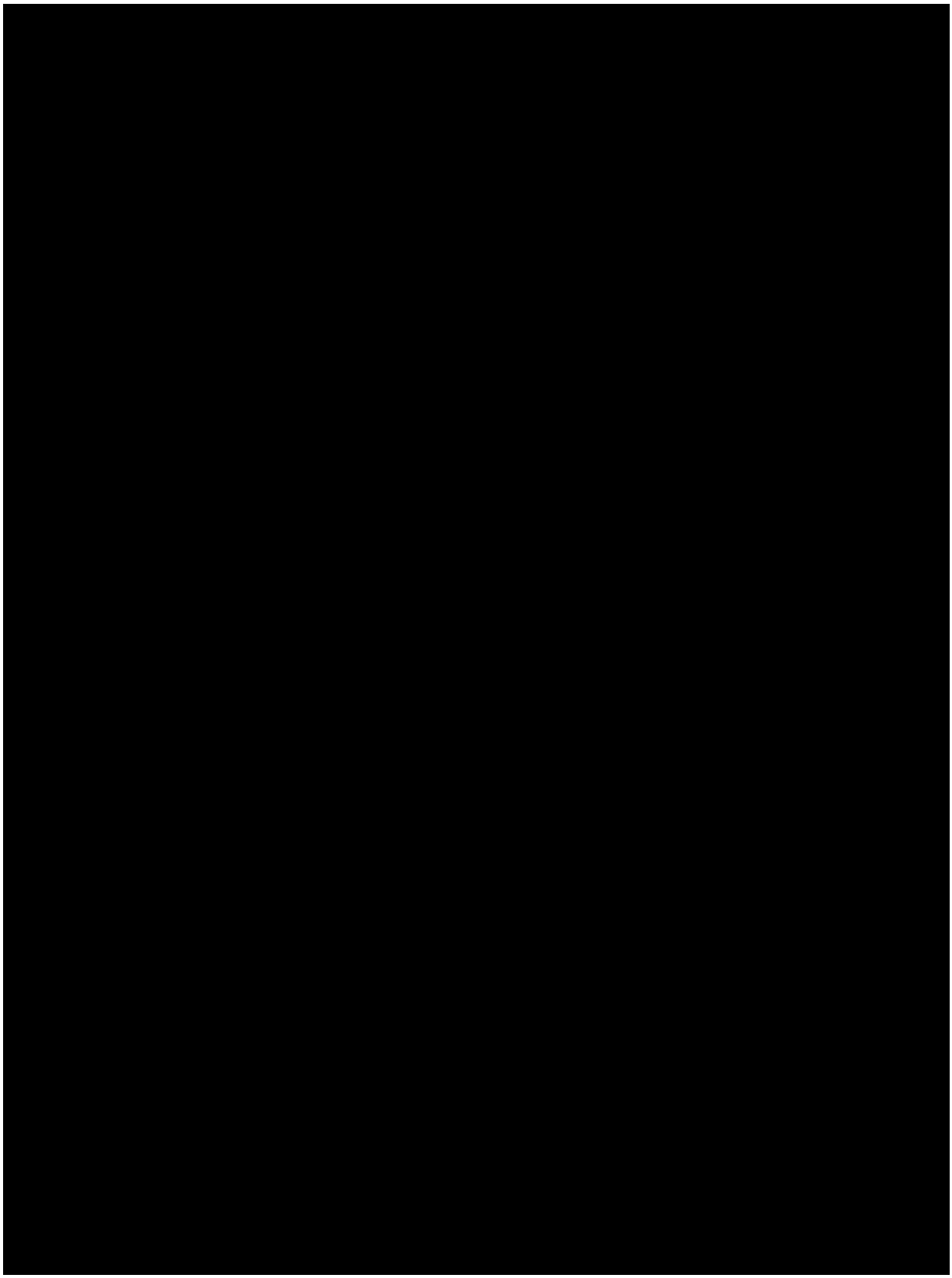
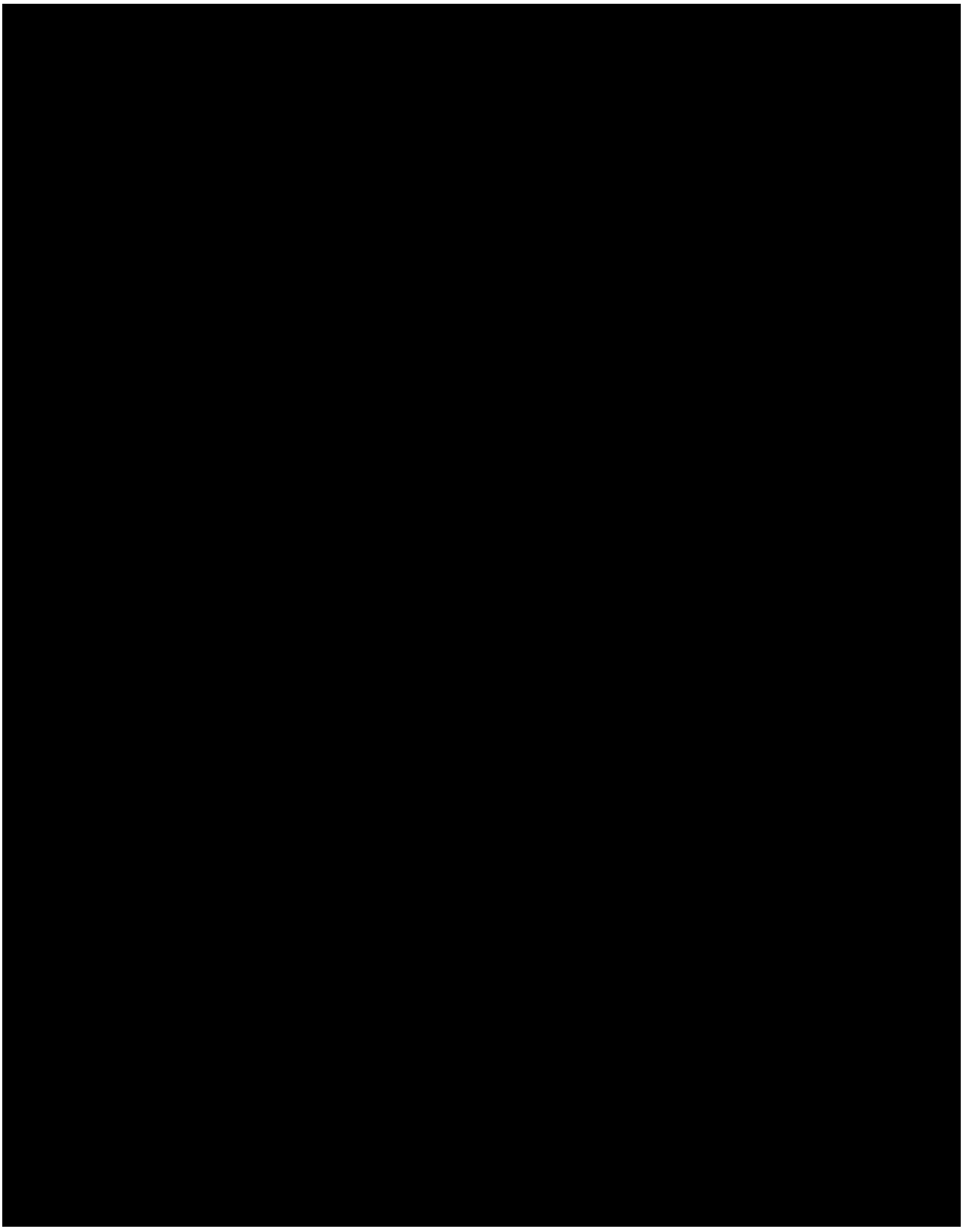




APPENDIX 3: PACKAGE INSERT

Drug Facts

Active ingredients
Ketotifen (0.025%)

(equivalent to ketotifen fumarate 0.035%)

Purpose
Antihistamine

Uses
Temporarily relieves itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

Warnings
For external use only

Do not use
- if solution changes color or becomes cloudy
- if you are sensitive to any ingredient in this product
- to treat contact lens related irritation

When using this product
- do not touch tip of container to any surface to avoid contamination
- remove contact lenses before use
- wait at least 10 minutes before reinserting contact lenses after use
- replace cap after each use

Stop use and ask doctor if you experience any of the following:
- eye pain
- changes in vision
- redness of the eyes
- itching worsens or lasts for more than 72 hours

Keep out of reach of children.

If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- **Adults and children 3 years of age and older:**
  Put 1 drop in the affected eye(s) twice daily, every 8–12 hours, no more than twice per day.
- **Children under 3 years of age:** Consult a doctor.

Other information

- Only for use in the eye.
- Store between 4°–25°C (39°–77°F).

Inactive ingredients

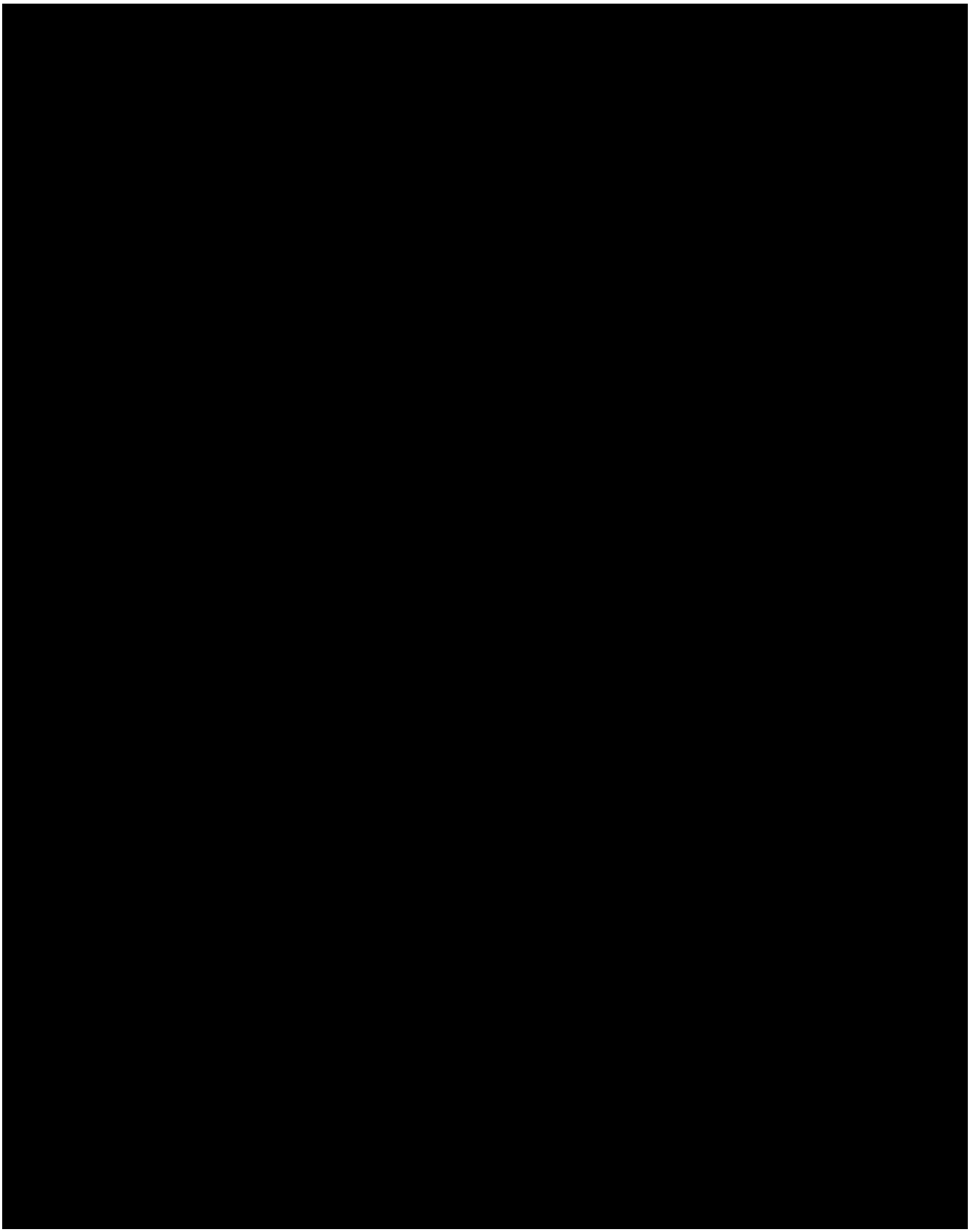
benzalkonium chloride 0.01%, glycerol, purified water, sodium hydroxide, and/or hydrochloric acid

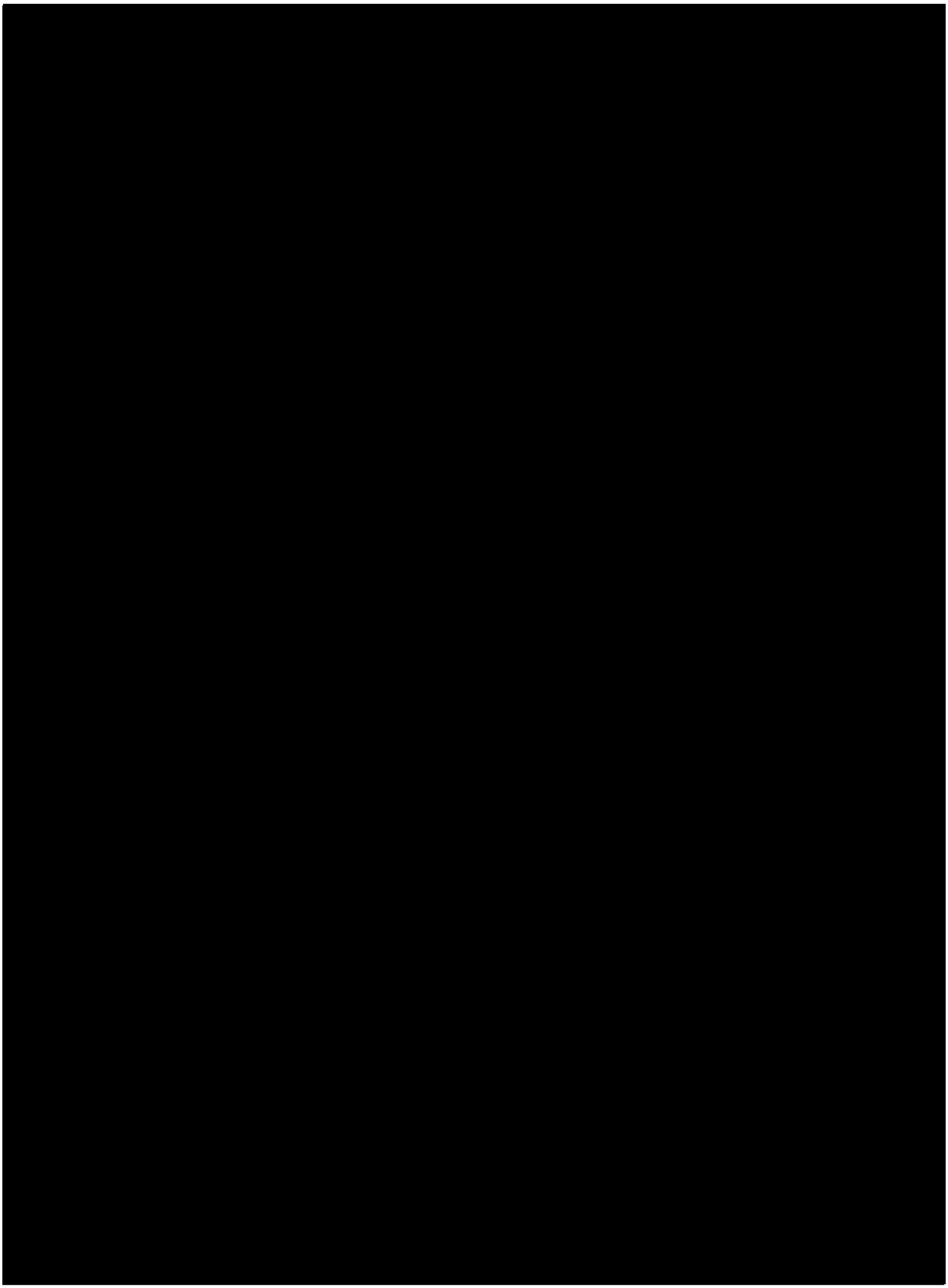
APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT 2 SUMMARY

Section	Page	Description of Change	Rationale
8.3.1.3 Visit 2 Procedures, 8.3.1.4 Visit 3 Procedures	30, 31	*Pre-CAC Ocular ~~Itching~~ and ~~Conjunctival Redness~~* ***Nasal Allergic Signs and Symptoms*** *Assessments:* The investigator and the subject will assess pre-CAC ocular ~~itching~~ and **nasal allergic signs and symptoms** ~~conjunctival redness~~ using the Ora-CAC® scales. Subjects exhibiting a sign and/or symptom of allergic conjunctivitis (defined as the presence of any itching or >1 conjunctival redness score in either eye) will be excluded.	Baseline of secondary efficacy measures will be captured at Visit 2 and 3 pre-CAC
8.3.1.3 Visit 2 Procedures	30	*Post-CAC Ocular Itching and Conjunctival Redness Assessments:* Assessments of itching will be made by the subject at 3(±1), 5(±1), and 7 (±1) minutes following allergen challenge. Assessments of ~~conjunctival~~ redness **and chemosis** will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge **and assessments of eyelid swelling, tearing/watery eyes, ocular mucous discharge, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge** (Appendix 2).	Additional measures captured at Visit 2
8.3.1.4 Visit 3 Procedures	31	*Post-CAC Ocular ~~Itching~~ and ~~Conjunctival Redness~~* ***Nasal Allergic Signs and Symptoms*** *Assessments:*	Update to procedure title





APPENDIX 8: INVESTIGATOR'S SIGNATURE

Protocol Title: A Single-Center Evaluation of the Relative Efficacy of EM-100 Compared to Zaditor® (Ketotifen Fumarate Ophthalmic Solution 0.035%) and Vehicle in the Treatment of Ocular Itching Associated with Allergic Conjunctivitis as Induced by the Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: 17-100-0011

Amendment Date: 04 April 2018

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>
<enter phone number>