CLINICAL TRIAL PROTOCOL: ST266-AC-201/16-100-0005

A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

NCT02978183

Protocol Date: 13 January 2017

Noveome Biotherapeutics, Inc.
100 Technology Drive, Suite 200
Pittsburgh, PA 15219

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Protocol Number:	ST266-AC-201/16-100-0005
Investigational Product Name:	ST266 Ophthalmic Drops
IND Number:	BB-IND 16,170
Indication Studied:	Allergic Conjunctivitis
Development Phase:	2
Name of Sponsor:	Noveome Biotherapeutics, Inc. 100 Technology Drive, Suite 200 Pittsburgh, PA 15219
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673
	Date
Original Protocol:	31 October 2016
Amendment:	13 January 2017

Statement of Compliance with Good Clinical Practice

This study will be performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP).

Confidentiality Statement

SPONSOR PERSONNEL

Chief Medical Officer/Medical Monitor:	[redacted]

ORA PERSONNEL

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

2 SYNOPSIS

Sponsor: Noveome Biotherapeutics, Inc.

Name of Finished Product: ST266

Name of Active Ingredient: Amnion-derived Cellular Cytokine Solution (ACCS)

Protocol Title: A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: ST266-AC-201/16-100-0005

Investigator: Multi-Center

Study Phase of Development: 2

Objectives:
To evaluate the efficacy of ST266 ophthalmic drops compared to placebo for the treatment of the signs and symptoms of allergic conjunctivitis.

Methodology:

Structure: Multi-center, double-masked, randomized, placebo-controlled, Phase 2, modified CAC study.

Duration: This study consists of nine (9) office visits over a period of approximately ten (10) days

Screening Period:

At the Screening Visit, subjects will sign the informed consent and an allergic skin test will be performed. At Visit 1, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration to at least one of the perennial allergens that the subject reacted positively to on his/her skin test. Subjects who elicit a positive CAC reaction will be scheduled to return to the office for repeat confirmatory CACs at Visits 2a and 2b. At Visit 3, subjects will undergo a baseline CAC to determine eligibility into this trial.

At-Home Treatment Period:

At Visit 3, a trained study technician will observe qualified subjects (or subject's caregiver) instill one (1) drop of assigned investigational product into each eye. Drop comfort assessments and drop description queries will be performed.

All subjects will be dispensed investigational product as well as a diary to bring home for daily use and completion. At-home dosing will begin the same day as Visit 3 approximately four (4) hours after their in-office dose. Subjects (or subject's caregiver) will continue at-home dosing four (4) times daily through Day 5.

In-Office Dosing:

A technician will instill one drop of investigational product in both eyes 15 minutes prior to each CAC at Visits 4a and 4b. Visit 4b will occur four (4) hours post Visit 4a. Subjects will be instructed to dose at home for the remaining doses to complete four (4) doses that day. A technician will instill one drop of investigational product in both eyes 15 minutes prior to CAC at Visit 5a.

Efficacy Evaluations:

The Duration of Action Efficacy Visit will be conducted at Visit 5b, [redacted] Subjects will receive an in-office dose [redacted] and will be instructed to take the remaining doses at home to complete four (4) doses that day.

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The Onset of Action Efficacy Visit will be conducted at Visit 6. The final dose of investigational product will be administered 15 minutes prior to the Visit 6 CAC.

Summary of Visit Schedule:

Screening Visit (Day -30 to -3)	Informed Consent/Skin Test/Washout Period
Visit 1 (Day -2):	Screening/Titration CAC
Visit 2a (Day -1):	CAC #1
Visit 2b (Day -1; 4 hours from Visit 2a):	CAC #2
Visit 3 (Day 1):	Baseline CAC/Enrollment/Begin QID Treatment
Visit 4a (Day 6):	CAC #1
Visit 4b (Day 6; 4 hours from Visit 4a):	CAC #2
Visit 5a (Day 7):	CAC #3
Visit 5b (Day 7; 4 hours from Visit 5a):	Duration of Action Efficacy CAC (4 Hours Post-Dose)
Visit 6 (Day 8):	Onset of Action Efficacy CAC (15 Minutes Post-Dose)

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. In addition, randomization will be stratified by [redacted] 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:

Up to 175 subjects will be screened in order to enroll approximately 70 subjects at two (2) centers.

Diagnosis

Allergic Conjunctivitis

Inclusion Criteria

Each subject must:

1) be at least 18 years of age 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 ocular allergies and a positive skin test reaction to a seasonal (individual grass allergen, individual tree allergen, and/or ragweed) AND perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test;
5) be able and willing to avoid all disallowed medication for the appropriate washout period and during

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the study (see exclusion 6);

6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to 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 at the exit visit[1]; must not be lactating; and must agree to use a medically acceptable form of birth control[2] throughout the study duration and for at least 14 days prior to instillation of investigational product (Visit 3)[3]. 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 [redacted]
9) have a positive bilateral post-CAC reaction [redacted] to a perennial allergen [redacted]
10) have a positive bilateral post-CAC reaction [redacted]
11) be able to self-administer eye drops satisfactorily or have a caregiver at home[4] routinely available for this purpose.

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, or pterygium);
3) have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;

[1] The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study.
[2] 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.
[3] 14 day birth control duration will be queried and captured at initial medical/medication history
[4] If a caregiver will be used to administer eye drops, then he/she must be present at Visit 3 to administer eye drops in-office.

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

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

45 Days
- depot-corticosteroids;

2 months
- immunotherapeutic agents: if on treatment at time of consent, treatment must have bee maintained steadily for at least 2 months prior; neither the immunotherapeutic agent nor it dosage may change during the clinical trial.

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

7) 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 the 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) manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visit 1 [redacted]
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.
12) have cancer or have a history of cancer within the last 5 years.

Test Product, Dose and Mode of Administration:
- ST266 Ophthalmic Drops

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Name of Finished Product: ST266

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Reference Therapy, Dose and Mode of Administration:

- Placebo (0.9% Sodium Chloride) Ophthalmic Drops

Criteria for Evaluation:

Efficacy Measures:

Primary:

- Ocular itching evaluated by the subject at all time [redacted]
- Conjunctival redness evaluated by the investigator at all time [redacted]

Secondary:

The following secondary efficacy assessments will occur pre-CAC and at [redacted] post-CAC [redacted]

- Ciliary redness evaluated by the investigator
- Episcleral redness evaluated by the investigator
- Chemosis evaluated by the investigator
- Eyelid swelling evaluated by the subject
- Tearing evaluated by the subject
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject
- A composite score of presence or absence of at least one nasal symptom evaluated by the subject

All assessments will be evaluated at pre-CAC and [redacted] minutes post-CAC [redacted]

Tolerability

- Drop comfort assessment [redacted] at Visit 3.
- Drop descriptor query [redacted] at Visit 3.

Exploratory:

- Conjunctival Inflammation Score (CIS) evaluated by a masked clinician using confocal microscopy post-CAC [redacted]
- Diary assessments for all subjects. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening from Visit 4b to Visit 6 [redacted]
- Digital photographs will be taken at-home of each eye of all subjects (at one center) prior to subjects completing diary assessments from Visit 4b to Visit 6.
- Digital photographs will be taken in-office of all subjects (at one center) at [redacted] minutes post-CAC at Visits 3, 5b, and 6.

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Safety Measures:

- Adverse Events
- Visual Acuity at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy

General Statistical Methods and Types of Analyses

[redacted]

Sample Size

[redacted]

Primary Efficacy Analyses

[redacted]

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[redacted]
Summary of Known and Potential Risks and Benefits to Human Subjects Refer to Investigator's Brochure (IB).

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LIST OF ABBREVIATIONS

AC	allergic conjunctivitis
ACCS	Amnion-derived Cellular Cytokine Solution
AE	adverse event
AMP	Amnion-derived Multipotent Progenitor
ANCOVA	Analysis of Covariance
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CIS	conjunctival inflammation score
CRF	case report form
CRO	contract research organization
DHHS	Department of Health and Human Services
ECD	endothelial cell density
ECG	Electrocardiogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
IB	investigators' brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional/independent review board
ITT	intent to treat

IV	intravenous
LASIK	laser in situ keratomileusis
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
NCS	not clinically significant
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
Ora-CAC®	conjunctival allergen challenge
OS	left eye
OU	both eyes
PHI	protected health information
PP	per protocol
PRN	as needed
QID	four times a day
ROPI	Report of Prior Investigations
SAE	serious adverse event
SAS	statistical analysis software
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedures
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
VA	visual acuity

3 INTRODUCTION

Allergies affect approximately 15% of the global population and up to 30% of the U.S. population (Bielory 2000). 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 (Abelson 2003). Histamine is the primary preformed mediator responsible for the typical 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 (Ciprandi 1993; Bacon 2000).

Current treatments for allergic conjunctivitis include histamine blockers and mast-cell stabilizers, which address early-phase symptoms, and steroids, which address late-phase symptoms. Agents that have good efficacy with fewer adverse effects, particularly associated with steroids for late-phase symptoms, are warranted.

Amnion-derived Multipotent Progenitor (AMP) cells have a unique secretory profile, producing a novel secretome containing many cytokines and growth factors known to be involved in wound healing and the inflammatory response. This secretome, known as ST266 (formerly Amnion-derived Cellular Cytokine Solution [ACCS], Noveome Biotherapeutics, Inc.), has been carefully characterized. Noveome produces ST266 under cGMP conditions. Placentas are tested and screened for known infectious agents, and conform to all HIPAA requirements. The secreted proteins have been characterized by mass spectroscopy, antibody array analysis, and ELISA. Lot release testing of individual production lots of ST266 have documented the concentration reproducibility of five selected cytokines (PDGF-ββ, VEGF, Angiogenin, TIMP-1, TIMP-2) and MMP-9 inhibition activity. ST266 may provide a novel treatment option for inflammatory conditions, including allergic conjunctivitis (Steed 2008).

ST266 has been shown to be anti-inflammatory, anti-apoptotic, and neuroprotective in several animal models, including rats, rabbits, guinea pigs, and mice. ST266 appears to reinstate physiologic homeostasis in impaired inflammatory conditions without the application of steroids and associated side effects. The scientific rationale for using this amnion cell-derived product originated from scarless fetal wound healing partially

attributed to cytokines in the amniotic fluid (Larson 2010, Lo 2012). Several *in vivo* animal studies showed faster wound healing with ST266, sometimes with less inflammation. In a mouse ear model of inflammation caused by a contact irritant, ST266 reduced inflammation similar to clobetasol, a class I steroid, by the third day. Nonclinical toxicology studies have been performed with topical (dermal, oral cavity, eyes) and systemic (IV) formulations of ST266, and no safety issues have been identified. When given topically in animal models, there was no evidence of systemic exposure to ST266 (Bergmann 2009).

ST266 has been shown to be safe in eight separate preclinical GLP safety studies of single and multiple repeat-dose administrations for topical applications. A 24-hour ocular pharmacokinetic (PK) and tissue distribution study conducted in 36 New Zealand white rabbits following topical and IV administration of ST266 (50 µL) found ST266 primarily in the lower conjunctiva, with no indication that the protein diffused in the vitreous or retina after topical dosing. Peak tissue concentrations were observed at 6 hours after dosing. At 24-hrs post-dosing, approximately 70% of the material remained in the vitreous, suggesting extended activity. In an acute eye irritation study with three (3) New Zealand white rabbits, topical administration of ST266 (0.1 mL) after 72 hours indicated that the drug was non-irritating (Investigational Brochure ST266, topical ophthalmic administration 2016).

ST266 has been studied in Phase 1 clinical trials involving topical administration to the skin or oral cavity. In these studies, ST266 was well tolerated and no safety issues were identified. Approximately 100 humans have been exposed to ST266 for up to 42 consecutive days without drug-related adverse effects in six (6) separate clinical trials. One (1) study showed anti-inflammatory efficacy in treating gingivitis. Another Phase 1 study with topical ST266 treatment in subjects with partial thickness burns indicated no evidence of systemic absorption of ST266 components. Noveome is currently conducting a Phase 2 randomized, double-blind, placebo-controlled 9-month safety and efficacy study of up to 150 subjects with periodontitis. Noveome completed a Phase 1 study (ST-05-14) to assess the safety of ST266 eye drops in subjects with moderate to severe dry eye. Thirty (30) subjects were randomized to receive either study drug or an over-the-counter artificial tear eye drops four times per day for six (6) weeks. Subjects were examined regularly during the six-week dosing period and then followed for an additional month for safety. No adverse events were observed related to administration of the study drug. No clinically significant changes were observed in best corrected visual acuity (BCVA), intraocular pressure (IOP), endothelial cell density (EDC), conjunctival staining, tear osmolarity, cup-to-disc ratio, hematology, blood chemistry, urinalysis, or vital signs after initiation of the investigational treatment. The results provide preliminary evidence of safety and tolerability of ST266 eye drops in human subjects.(Investigational Brochure ST266 topical ophthalmic administration 2016).

The conjunctival allergen challenge (CAC)-induced allergic response mimics the acute response that is triggered by intermittent exposure to allergen. The Ora-CAC® model has been used to evaluate anti-allergic agents and to identify the cellular and mediator responses seen in allergic conjunctivitis (Abelson et al 1990). The Ora-CAC® model has

been clinically validated and has been recognized by the U.S. FDA as a reliable method for evaluating novel ophthalmic pharmaceutical drugs (Abelson and Loeffler 2003). Since changes in the signs and symptoms of ocular allergy are captured on standardized severity scales, the CAC model allows for precise comparisons of the effects of ocular allergy drugs among study subjects with a high level of internal control, sensitivity, and reproducibility.

The modified CAC model has been developed to study the interactions between the early and late phases of the allergic response in the eye, and to evaluate the effects of pharmaceutical intervention. The modified CAC model uses additional challenges conducted over a longer time interval to evaluate the effectiveness of a test agent to 1) prevent an acute ocular allergic reaction (the initial CAC), and 2) evaluate the test agent's ability to prevent an acute ocular allergic reaction in the presence of subclinical late-phase inflammation (the latter re-challenge CACs). The modified CAC model provides the opportunity to investigate the effects of the underlying inflammatory reaction on the ability of tissues to mount a robust acute response to a subsequent allergen challenge. The modified CAC model also provides a means to investigate the mechanism(s) of action of anti-inflammatory agents in the treatment of both acute and chronic allergic reactions.

Noveome Biotherapeutics, Inc. is proposing to conduct a multi-center, double-masked, randomized, placebo-controlled, Phase 2 study of the effectiveness of ST266 compared to placebo for the treatment of allergic conjunctivitis using the modified Ora-CAC® model.

4 STUDY OBJECTIVES

To evaluate the efficacy of ST266 ophthalmic drops compared to placebo for the treatment of the signs and symptoms of allergic conjunctivitis.

5 CLINICAL HYPOTHESES

It is hypothesized that ST266 ophthalmic drops will be [redacted]

6 OVERALL STUDY DESIGN

This is a multi-center, double-masked, randomized, placebo-controlled, Phase 2, modified conjunctival allergen challenge study using the Ora-CAC® model. At Visit 3, subjects will be randomly assigned [redacted] to one of the following treatment arms:

- ST266 Ophthalmic Drops [redacted]
- Placebo (0.9% sodium chloride) Ophthalmic Drops [redacted]

At Visit 3, a trained study technician will observe qualified subjects (or subject's caregiver) instill one (1) drop of assigned investigational product into each eye. Drop comfort assessments and drop description queries will be performed.

All subjects will be dispensed investigational product as well as a diary to bring home for daily use and completion. At-home dosing will begin the same day as Visit 3 approximately [redacted] after their in-office dose. Subjects will be instructed to dose at home for the two to three (2-3) remaining doses that day. Subjects (or subject's caregiver) will continue at-home dosing four (4) times daily through Day 5.

At Visits 4a and 4b, a technician will instill one drop of investigational product in both eyes [redacted] prior to each CAC; the 2nd CAC will be [redacted] post Visit 4a. Subjects will be instructed to dose at home for the remaining doses to complete four (4) doses that day.

The Duration of Action Efficacy Visit will be conducted at Visit 5b, [redacted] after in-office dosing [redacted] Subjects will receive an in-office dose [redacted] post Visit 5b Duration of Action CAC and will be instructed to take the remaining doses at home to complete four (4) doses that day.

The Onset of Action Efficacy Visit will be conducted at Visit 6. The final dose of investigational product will occur [redacted] prior to the Visit 6 Onset of Action CAC. A subset of ten (10) subjects at one (1) center will have confocal microscopy performed in one (1) eye following the CAC assessments at this visit.

[redacted]

7 STUDY POPULATION

7.1 NUMBER OF SUBJECTS (APPROXIMATE)

Up to 175 subjects will be screened in order to enroll approximately 70 subjects at two (2) centers.

7.2 STUDY POPULATION CHARACTERISTICS

Subjects at least 18 years of age, of either gender or any race, who have a positive history of allergic conjunctivitis, and who meet all of the inclusion criteria and none of the exclusion criteria.

7.3 INCLUSION CRITERIA

Each subject must:

1) be at least 18 years of age 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 ocular allergies and a positive skin test reaction to a seasonal (individual grass allergen, individual tree allergen, and/or ragweed) AND perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test;
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 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 at the exit visit[5]; must not be lactating; and must agree to use a medically acceptable form of birth control[6] throughout the study duration and for at least 14 days prior to instillation of investigational product (Visit 3)[7]. 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 [redacted]
9) have a positive bilateral post-CAC reaction [redacted]
10) have a positive bilateral post-CAC reaction [redacted]
11) be able to self-administer eye drops satisfactorily or have a caregiver at home[8] routinely available for this purpose.

7.4 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, or pterygium);
3) have had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months;

[5] The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study.
[6] 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.
[7] 14 day birth control duration will be queried and captured at initial medical/medication history
[8] If a caregiver will be used to administer eye drops, then he/she must be present at Visit 3 to administer eye drops in-office.

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

14 Days

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

45 Days

- depot-corticosteroids;

2 months

- immunotherapeutic agents: if on treatment at time of consent, treatment must have been maintained steadily for at least 2 months prior; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

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

7) 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 the 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) manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visit 1 [redacted];
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;
12) have cancer or have a history of cancer within the last 5 years.

7.5 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.

Sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 10.6.2).

8 STUDY MEASURES

8.1 EFFICACY MEASURES

8.1.1 Primary Efficacy Measure(s)

- Ocular itching evaluated by the subject at all time points [redacted] at Visits 5b and 6.
- Conjunctival redness evaluated by the investigator at all time points [redacted] at Visits 5b and 6.

8.1.2 Secondary Efficacy Measure(s)

The following secondary efficacy assessments will occur at pre-CAC and [redacted] post-CAC [redacted] at Visits 5b and 6:

- Ciliary redness evaluated by the investigator
- Episcleral redness evaluated by the investigator
- Chemosis evaluated by the investigator
- Eyelid swelling evaluated by the subject
- Tearing evaluated by the subject
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject

- A composite score of presence or absence of at least one nasal symptom evaluated by the subject

All assessments will be evaluated at pre-CAC and [redacted] post-CAC at Visits 4a, 4b, and 5a.

8.1.3 Criteria for Effectiveness

This clinical study is designed to evaluate the efficacy of ST266 ophthalmic drops compared to placebo for the treatment of the signs and symptoms of allergic conjunctivitis.

To demonstrate efficacy for ocular itching and conjunctival redness, ST266 ophthalmic drops need to show clinical superiority over placebo by at least 0.5 units of a 5 point scale for all three (3) post-CAC time points: [redacted] post-CAC for itching and [redacted] post-CAC for conjunctival redness, and at least 1 unit for the majority (2:3) of these post-CAC time points for each primary endpoint.

If ocular itching meets statistical significance and the criteria for clinical efficacy as defined above, then the study will be considered a success for ocular itching. In addition, if conjunctival redness then also meets statistical significance and the criteria above for clinical success, then the study will be considered a success for both ocular itching and conjunctival redness.

8.2 SAFETY MEASURES

- Adverse Events
- Visual Acuity at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy

8.3 EXPLORATORY MEASURES

- Conjunctival Inflammation Score (CIS) evaluated by a masked clinician using confocal microscopy post-CAC [redacted]
- Diary assessments for all subjects. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening from Visit 4b to Visit 6 [redacted]
- Digital photographs will be taken at-home of each eye of all subjects (at one center) prior to subjects completing diary assessments from Visit 4b to Visit 6.
- Digital photographs will be taken in-office of all subjects (at one center) at [redacted] post-CAC at Visits 3, 5b, and 6.

8.4 TOLERABILITY MEASURES

- Drop comfort assessment [redacted] at Visit 3
- Drop descriptor query [redacted] at Visit 3

9 STUDY MATERIALS

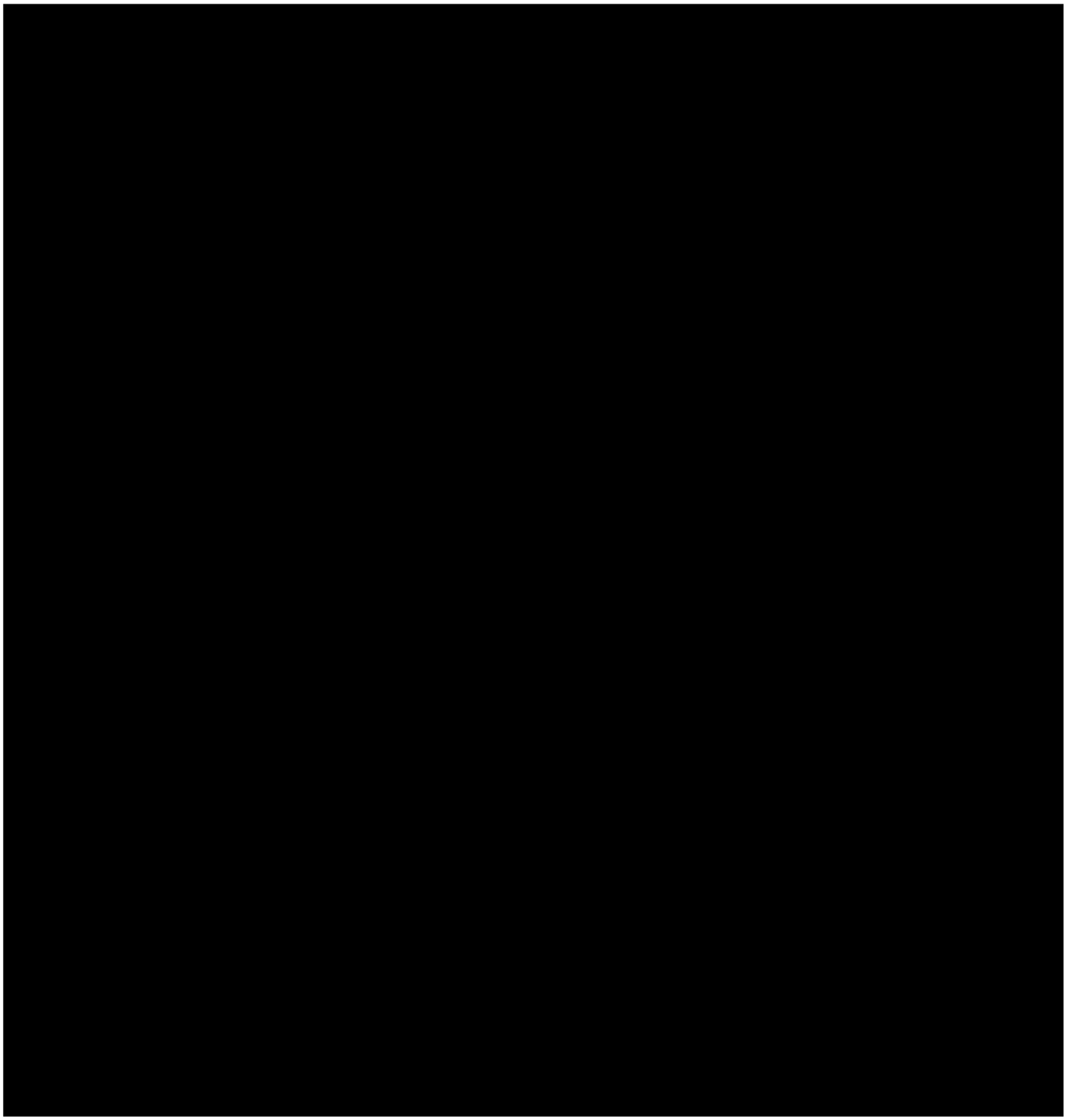
9.1 STUDY TREATMENT(S)

9.1.1 Study Treatment(s)/ Formulation(s)

- ST266 Ophthalmic Drops
- Placebo (0.9% Sodium Chloride) Ophthalmic Drops

[redacted]

[redacted]



[redacted]

9.1.2 Instructions for Use and Administration

[redacted]

[redacted]

9.2 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, cockroach, dust mites, individual species of grasses, individual species of trees, and/or ragweed)
- The ocular anesthetic agent (Fluress) and dilating drops used for the intraocular pressure and dilated fundus examination, respectively
- The ocular anesthetic agent (proparacaine hydrochloride ophthalmic solution) used for the confocal microscopy
- Relief drops

10 STUDY METHODS AND PROCEDURES

10.1 SUBJECT ENTRY PROCEDURES

10.1.1 Overview

Subjects as defined by the criteria in section 7.2, 7.3, and 7.4 will be considered for entry into this study.

10.1.2 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 (IRB).

Informed consent may be obtained prior to Visit 1 if the subject wishes to review and discuss the Informed Consent with the Investigator or wishes to get a skin test prior to

Visit 1. However, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

- Proper washout of certain medications is necessary
- Sufficient time of discontinuation of contact lens wear is necessary
- Post-operative period

Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

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.

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

14 Days

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

45 Days

- depot-corticosteroids;

2 months

- immunotherapeutic agents: if on treatment at time of consent, treatment must have been maintained steadily for at least 2 months prior; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

10.1.4 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.

10.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the study who sign a consent form will be assigned a screening number which will be entered on 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 combinations, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

Once a subject meets all qualification criteria at Visit 3 (Day 1), he/she will be randomized to one of two treatment arms [redacted] assignment ratio. Subjects will be assigned the lowest four (4) digit randomization number available at the Investigative site within the appropriate stratum. [redacted] No randomization numbers will be skipped or omitted.

10.2 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.

10.2.1 Prohibited Medications/Treatments

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

- depot-corticosteroids;
- immunotherapeutic agents: if on treatment at time of consent, treatment must have been maintained steadily for at least 2 months prior; neither the immunotherapeutic agent nor its dosage may change during the clinical trial.

10.2.2 Escape Medications

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 at the end of the subject's last visit, after all evaluations are completed.

10.2.3 Special Diet or Activities

Not Applicable.

10.3 EXAMINATION PROCEDURES

Procedures to be performed at each study visit with regard to study objective(s)

10.3.1 **Screening Visit (Day -30 to -3): Informed Consent/Skin Test/Washout Period**

- *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.

  Informed consent may be obtained prior to Visit 1 if the subject wishes to review and discuss the Informed Consent with the Investigator or wishes to get a skin test prior to Visit 1. However, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

  - Proper washout of certain medications is necessary
  - Sufficient time of discontinuation of contact lens wear is necessary
  - Post-operative period

  Medical/medication history, demographics, skin test, and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1, but must be confirmed at Visit 1 (with the exception of demographics and skin test).

- *Allergic Skin Test*: A diagnostic test for allergic disease (skin test) will be performed.

- *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 the 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 10.1.3)

- *Schedule Visit 1:* Qualifying subjects will be scheduled for Visit 1. If a subject did not meet a 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 three times.

10.3.2 **Visit 1 (Day -2): Screening/Titration CAC**

- *Informed Consent/HIPAA (for subjects who did not come in for a Screening Visit):* 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.

- *Allergic Skin Test (for subjects who did not come in for a Screening Visit):* A diagnostic test for allergic disease (skin test) will be performed.

- *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 the 45 days prior to Visit 1.

  If subjects came in for a Screening Visit prior to Visit 1, medical/medication history and inclusion/exclusion review must be reviewed and confirmed at Visit 1.

- *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 and for at least 14 days prior to the instillation of investigational product (Visit 3).

Note: 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.

- *Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of [redacted] in order to qualify.

- *Initial Ocular and Nasal Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess initial ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2). Subjects exhibiting signs and/or symptoms of allergic conjunctivitis [redacted] will be excluded.

- *Slit Lamp Biomicroscopy:* A slit-lamp exam 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:* Confirm if subject needs to washout from any current medications and instruct he/she to follow the appropriate washout time periods (refer to Section 10.1.3)

- *Titration Conjunctival Allergen Challenge*: A conjunctival allergen challenge (CAC) will be performed bilaterally with a perennial allergen (cat dander, dog dander, cockroach, dust mite) that has been serially diluted in buffered saline and administered via a micropipette. [redacted] If increasing doses are required (i.e., for insufficient bilateral itching as assessed by the subject and/or redness as evaluated by the Investigator), doses may be skipped. If a positive CAC reaction is not elicited with the first allergen, other allergens to which the subject is sensitized may be used starting at the lowest dose.

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

[redacted]

- *IOP Measurement:* For subjects eliciting a positive post-CAC reaction, intraocular pressure (IOP) will be measured in each eye by contact tonometry.

- *Dilated Fundus Examination*: For subjects eliciting a positive post-CAC reaction, a dilated fundus examination will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology. Findings of abnormality which are not exclusionary should be recorded as Medical History.

- *Review of Inclusion/Exclusion Criteria*

- *Schedule Visit 2a:* Qualifying subjects will be scheduled for Visit 2a the following day.

10.3.3 **Visit 2a (Day -1): CAC #1**

- *Update of Medical/Medication History*

- *Visual Acuity Utilizing an ETDRS Chart*

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess pre-CAC ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2).

- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions.

- *Review of Inclusion/Exclusion Criteria*

- *Conjunctival Allergen Challenge (CAC) #1:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2) approximately [redacted] following the CAC.

- *Schedule for Visit 2b:* Subjects will be asked to return to the office 3 ½ hours after the allergen challenge. Subjects will be allowed to leave the clinic and will be instructed to avoid allergens, which may trigger an ocular allergic response.

10.3.4 **Visit 2b (Day -1; 4 hours from Visit 2a): CAC #2**

- *Update of Medical/Medication History*
- *Visual Acuity Utilizing an ETDRS Chart*
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions.
- *Review of Inclusion/Exclusion Criteria*
- *CAC #2:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally. Challenge will occur [redacted] following the challenge at Visit 2a.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2) approximately [redacted] following CAC.
- *Schedule for Visit 3:* Subjects will be scheduled for Visit 3 the following day.

10.3.5 **Visit 3 (Day 1): Baseline CAC/Enrollment/Begin QID Treatment**

- *Update of Medical/Medication History*
- *Visual Acuity Utilizing an ETDRS Chart*
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions.
- *Review Inclusion and Exclusion Criteria*
- *Baseline CAC:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally.
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessments of itching will be made by the subject at [redacted] following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be

made by the subject at [redacted] post-challenge (Appendix 2). If the subject fails to react positively [redacted] in both eyes in 2 out of the first 3 time points, he/she will be excluded from the study.

- *Digital Photographs* ***(for subjects at one center)****:* Digital photographs may be taken of each eye at [redacted] post-challenge.

- *Tear Collection* ***(for subjects at one center)****:* Up to [redacted] of tears / eye may be collected from the inferior temporal tear meniscus of each participant.

- *Review of Inclusion/Exclusion Criteria*

- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be assigned a 4-digit subject number. Subjects will be randomized by assignment of the lowest randomization number available at the site. [redacted] No numbers will be skipped or omitted.

- *Investigational Product Instillation:* A trained study technician will observe the subject (or subject's caregiver) instill investigational product according to the directions for use. The investigational product kit number and the time of instillation will be recorded.

- *Drop Comfort Evaluation:* [redacted] (Appendix 2).

- *Drop Descriptor Query:* [redacted] (Appendix 2).

- *Investigational Product and Dosing Diary Dispensation:* Enrolled subjects (or subject's caregiver) will be instructed to instill one drop of the assigned investigational product in each eye four (4) times daily approximately every [redacted], in the same calendar day (no earlier than [redacted] from previous dose) beginning the day of Visit 3, up until their Visit 4a. Subjects will be instructed to dose at least two to three (2-3) more times at home on the day of Visit 3 depending on the time of their Visit 3. Subjects will also be dispensed a dosing diary to record the time each at-home dose is taken.

  Subjects will also be instructed to bring both investigational product and the dosing diary to the next visit (Visit 4a) for a compliance check. Subjects will be instructed to dose approximately [redacted]

prior to their Visit 4a appointment, if time permits. If they are unable to dose prior to their appointment, they will receive their first dose in office that day.

- *Adverse Event Query*
- *Schedule for Visit 4a:* Subjects will be scheduled for Visit 4a, which will be five (5) days later.

10.3.6 **Visit 4a (Day 6): CAC #1**

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Investigational Product and Dosing Diary Review and Collection*: Investigational product and dosing diary will be collected and reviewed for compliance and to address any queries.

  IP dosing compliance from Visit 3 to Visit 4a will be determined by the amount of doses taken. [redacted] These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from Visit 1 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation*: A trained study technician will instill investigational product approximately [redacted] prior to CAC #1 according to the directions for use. The investigational product kit number and the time of instillation will be recorded.
- *CAC #1:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally [redacted] post instillation of investigational product.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2) approximately [redacted] following CAC.

- *Adverse Event Query*

- *Schedule for Visit 4b:* Subjects will be asked to return to the office 3 ½ hours after investigational product instillation. Subjects will be allowed to leave the clinic and will be instructed to avoid allergens, which may trigger an ocular allergic response.

10.3.7 Visit 4b (Day 6; 4 hours from Visit 4a): CAC #2

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from Visit 1 will be considered an adverse event.

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*

- *Slit Lamp Biomicroscopy*

- *Investigational Product Instillation:* A trained study technician will instill investigational product approximately [redacted] prior to CAC #2 according to the directions for use. The investigational product kit number and the time of instillation will be recorded.

- *CAC #2:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally approximately [redacted] from the conjunctival allergen challenge at Visit 4a.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2) approximately [redacted] following CAC.

- *Investigational Product and Dosing Diary Dispensation:* All subjects (or subject's caregiver) will be instructed to continue instilling one drop of the assigned investigational product in each eye approximately every [redacted] in the same calendar day [redacted] Subjects will be instructed to take the remaining doses at home to complete four

(4) doses that day. Subjects will also be dispensed a dosing diary and will be instructed to complete daily assessments prior to bedtime and upon awakening beginning the evening of Visit 4b.

Subjects will also be instructed to bring both investigational product and diary to the next visit (Visit 5a) for a compliance check. Subjects will be instructed to dose approximately [redacted] prior to their Visit 5a appointment, if time permits. If they are unable to dose prior to their appointment, they will receive their first dose in office that day.

Subjects at one center will be instructed to take photographs of both of their eyes prior to completing diary assessments.

- *Adverse Event Query*
- *Schedule for Visit 5a:* Subjects will be scheduled for Visit 5a the following day.

10.3.8 **Visit 5a (Day 7): CAC #3**

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Investigational Product and Dosing and Assessments Diary Review and Collection*: Investigational product and dosing and assessments diary will be collected and reviewed for compliance from Visit 4b to Visit 5a and to address any queries.
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from Visit 1 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation*: A trained study technician will instill investigational product approximately [redacted] prior to CAC #3 according to the directions for use. The investigational product kit number and the time of instillation will be recorded.
- *CAC #3:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally [redacted] post instillation of investigational product.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* The Investigator and the subject will assess ocular and nasal allergic signs and symptoms using the Ora-CAC® scales (see Appendix 2) approximately [redacted] following CAC.

- *Adverse Event Query*

- *Schedule for Visit 5b:* Subjects will be asked to return to the office 3 ½ hours after investigational product instillation. Subjects will be allowed to leave the clinic and will be instructed to avoid allergens, which may trigger an ocular allergic response.

10.3.9 Visit 5b (Day 7; 4 hours from Visit 5a): Duration of Action Efficacy CAC (4 Hours Post-Dose)

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from Visit 1 will be considered an adverse event.

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*

- *Slit Lamp Biomicroscopy*

- *Duration of Action Conjunctival Allergen Challenge* [redacted]*:* For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally. Challenge will occur approximately [redacted] from the time of investigational product instillation at Visit 5a.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at [redacted] following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at [redacted] (Appendix 2).

- *Digital Photographs **(for subjects at one center)**:* Digital photographs may be taken of each eye at [redacted] post-challenge.

- *Investigational Product Instillation*: A trained study technician will instill investigational product [redacted] after the Duration of Action CAC

(after all post-CAC assessments have been completed) according to the directions for use. The investigational product kit number and the time of instillation will be recorded.

- *Investigational Product and Dosing Diary Dispensation:* All subjects (or subject's caregiver) will be instructed to continue instilling one drop of the assigned investigational product in each eye approximately [redacted] Subjects will be instructed to take the remaining doses at home to complete four (4) doses that day. Subjects will also be dispensed a dosing diary and will be instructed to complete their daily assessments prior to bedtime and upon awakening until the morning of Visit 6.

  Subjects will also be instructed to bring both investigational product and diary to the next visit (Visit 6) for a compliance check and not to dose on the day of their Visit 6 appointment. They will receive their final dose in-office.

  Subjects at one center will be instructed to take photographs of both of their eyes prior to completing diary assessments.

- *Adverse Event Query*

- *Schedule for Visit 6:* Subjects will be scheduled for Visit 6 the following day.

10.3.10 Visit 6 (Day 8): Onset of Action Efficacy CAC (15 Minutes Post-Dose)

- *Update of Medical/Medication History*

- *Adverse Event Query*

- *Investigational Product and Dosing and Assessments Diary Review and Collection*: Investigational product and dosing and assessments diary will be collected and reviewed for compliance from Visit 5b to Visit 6 and to address any queries.

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

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from Visit 1 will be considered an adverse event.

- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*

- *Slit Lamp Biomicroscopy*

- *Investigational Product Instillation*: A trained study technician will instill investigational product approximately [redacted] prior to the Onset of Action CAC according to the directions for use. The investigational product kit number and the time of instillation will be recorded.

- *Onset of Action Conjunctival Allergen Challenge* [redacted] For each qualified subject, one drop of the allergen solution, of the same dose that elicited a positive reaction at Visit 1, will be administered bilaterally. Challenge will occur [redacted] from the time of investigational product instillation.

- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at [redacted] following allergen challenge. Assessments of redness and chemosis will be graded by the investigator and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at [redacted] (Appendix 2).

- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed following the completion of all post-CAC assessments.

- *Digital Photographs **(for subjects at one center)**:* Digital photographs may be taken of each eye at [redacted] post-challenge.

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease [redacted] from the Screening Visit will be considered an adverse event.

- *Confocal Microscopy **(subset of 10 subjects at one center)**:* Subjects' Conjunctival Inflammation Score (CIS) will be evaluated by a masked clinician approximately [redacted] post-CAC (after all signs and symptoms have been assessed), as outlined in Appendix 2.

- *Tear Collection **(for subjects at one center)**:* Up to [redacted] of tears / eye may be collected from the inferior temporal tear meniscus of each participant.

- *IOP Measurement:* Intraocular Pressure (IOP) will be measured in each eye by contact tonometry. [redacted] will be considered an Adverse Event.

- *Dilated Fundus Examination*

- *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*
- *Exit the Study*

Adverse Events will be monitored throughout the study. All adverse events will be promptly reviewed by the Investigator for accuracy and completeness. All adverse events will be documented on the appropriate electronic case report form.

10.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

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

If a subject is discontinued at a scheduled study visit (i.e. Visits 3, 4a, 4b, 5a, 5b, or 6) the remaining assessments should be captured on the Unscheduled Visit/Early Exit Visit pages of the source document and corresponding eCRF.

10.4.2 Unscheduled/Early Exit Visits

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) or Early Exit 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
- Intraocular Pressure Examination
- Dilated Fundus Examination

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

10.5 COMPLIANCE WITH PROTOCOL

Subjects who are inappropriately enrolled may be discontinued from the study. The reason for such discontinuation will be recorded as "protocol violation" in the source document and on the appropriate page in the electronic case report form (eCRF).

[redacted]

[redacted]

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, 2a, 2b, 3, 4a, 4b, 5a, 5b, and 6.

10.6 SUBJECT DISPOSITION

10.6.1 Completed Subjects

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

10.6.2 Discontinued Subjects

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

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

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

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

10.7 STUDY TERMINATION

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

10.8 STUDY DURATION

This study consists of nine (9) office visits over a period of approximately ten (10) days.

10.9 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 study drug/device 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.

11 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (eg, 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 (eg, off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

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 (1) comprehensive event. Any pre-existing medical condition that worsens after administration of study medication will also be considered an adverse event. Study medication includes the drug under evaluation or any other medications required by the protocol given during any stage of the study.

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).

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, 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.

11.1.1 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.

11.1.2 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 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. A not suspected AE can further be defined as:

  - *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.

Types of evidence that would suggest a causal relationship between the IP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (eg, 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 (eg, 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.

11.1.3 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 Report of Prior Investigations (ROPI) or is not listed at the specificity or severity that has been observed.

- *Expected*: an AE that is listed in the IB or ROPI at the specificity and severity that has been observed.

- *Not applicable:* an AE unrelated to the IP.

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

11.2 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;

  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;

  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 (eg, 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.

11.3 PROCEDURES FOR REPORTING ADVERSE EVENTS

All AEs and their outcomes must be reported to Ora, the study 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.

11.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

11.3.2 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 eCRF. 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. Additionally, in this study there are no expected SAEs and all SAEs will be considered suspected unexpected serious adverse reactions (SUSARs).

In the event of a SAE, the Investigator must notify Ora and the Sponsor Medical Monitor 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's Medical Monitor with a complete case history, which includes a statement as to the relationship to the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

11.4 PROCEDURES FOR UNMASKING (IF APPLICABLE)

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

11.5 TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

The Investigator will follow unresolved adverse events to resolution until the patient is lost to follow-up or until the adverse event is otherwise explained. Resolution means the patient has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the adverse event. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient 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.

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.

12 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

12.1 STATISTICAL ANALYSIS PLAN

The material described in this section is the basis for the Statistical Analysis Plan (SAP) for this study. The SAP will detail all analyses that will be performed and may include additional exploratory analyses not explicitly mentioned in the following sections. The SAP may be revised during the study to accommodate Clinical Trial Protocol

Amendments and to make changes to adapt to unexpected issues in study execution and/or data that affect the planned analyses. Any deviations from the final SAP will be provided in the final clinical study report.

12.2 STUDY POPULATIONS

12.2.1 Intent-to-Treat Population

[redacted]

12.2.2 Per-Protocol Population

[redacted]

12.2.3 Safety Population

[redacted]

12.3 STATISTICAL HYPOTHESES

[redacted]

12.4 SAMPLE SIZE

[redacted]

12.5 EFFICACY ANALYSES

[redacted]

12.6 SAFETY ANALYSIS

[redacted]

12.7 INTERIM ANALYSIS

No interim analyses are planned.

13 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 investigational products in the countries involved will be adhered to.

13.1 PROTECTION OF HUMAN SUBJECTS

13.1.1 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 (eg, due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

Informed consent may be obtained prior to Visit 1 if the subject wishes to review and discuss the Informed Consent with the Investigator or wishes to get a skin test prior to Visit 1. However, informed consent must be obtained prior to Visit 1 if any of the following criteria are determined during the telephone screening process:

- Proper washout of certain medications is necessary
- Sufficient time of discontinuation of contact lens wear is necessary
- Post-operative period

Medical/medication history, demographics, skin test and inclusion/exclusion review may be performed at the time of informed consent signing prior to Visit 1 (Screening Visit), but must be confirmed at Visit 1 (with the exception of demographics and skin test).

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Ora and/or study sponsor and provided in writing by Ora and/or study sponsor prior to the consent process.

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 three times.

13.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board 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/ERC approved version of the ICF will be used.

13.2 ETHICAL CONDUCT OF THE STUDY

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

13.3 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 in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study 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 investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

13.4 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 electrocardiograms. The Investigator's copy of the eCRFs serves as the Investigator's record of a subject's study-related data.

13.4.1 Retention of Documentation

All study related correspondence, subject records, ICFs, record of the distribution and use of all IPs and copies of eCRFs should be maintained on file for at least 2 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 2 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.

13.5 LABELING, PACKAGING, STORAGE, ACCOUNTABILITY, AND RETURN OR DISPOSAL OF INVESTIGATIONAL PRODUCT

13.5.1 Labeling/Packaging

ST266 and placebo will be provided to the clinical site(s) in [redacted] One ready-to-use ampoule is intended per treatment per subject. Once an ampoule is opened, it is not to be re-used.

13.5.2 Storage of Investigational Product

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

13.5.3 Accountability of Investigational Product

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

The Investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP dispensed to subjects, amount of IP returned to the Investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP.

13.5.4 Return or Disposal of Investigational Product

All IP 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.

13.6 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 (eg, 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.

13.7 HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

13.8 PUBLICATIONS

Publication will be in accordance with the terms of Section 6 – Publicity and Publication set forth in the Master Service Agreement, (the "AGREEMENT) dated October 07, 2016.

14 REFERENCES

Abelson MB. Loeffler O. Conjuctival allergen challenge: Models in the investigation of ocular allergy. Curr Allergy Asthma Reports 2003;3:363-368.

Abelson M B, Chambers WA, Smith LM. Conjunctival allergen challenge. a clinical approach to studying allergic conjunctivitis. Arch Ophthalmol 1990;108(1):84-88.

Bacon AS, Ahluwalia P, Irani AM, Schwartz LB, Holgate ST, Church MK, McGill JI. Tear and conjunctival changes during the allergen-induced early- and late-phase responses. J Allergy Clin Immunol 2000;106(5):948-954.

Bergmann J, Hackl F, Koyama T, Aflaki P, Smith C, Robson M, Eriksson E. The effect of amnion-derived cellular cytokine solution on the epithelialization of partial-thickness donor site wounds in normal and streptozotocin-induced diabetic swine. EPlasty 2009;9, online Oct 20, 2009.

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

C. S. Foster, R. Davanzo, T. E. Flynn, K. McLeod, R. Vogel, and R. S. Crockett, "Durezol (Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis.," J Ocul Pharmacol Ther, vol. 26, no. 5, pp. 475–483, Oct. 2010.

Ciprandi GS, Buscaglia G, Pesce P, Bagnasco M, Canonica GW. Ocular challenge and hyperresponsiveness to histamine in patients with allergic conjunctivitis. J Allergy Clin Immunol 1993;91(6): 1227-1230.

Investigational Brochure ST266. Oct 26, 2016, edition 8.

Larson BJ, Longaker MT, Lorenz HP. Scarless fetal wound healing: A basic science review. Plast Reconstr Surg 2010;126(4): 1172-1180.

Lo DD, Zimmermann AS, Nauta A, Longaker MT, Lorenz HP. Scarless fetal skin wound healing update. Birth Defects Research (Part C) 2012;96(3): 237-247.

Steed DL, Trumpower C, Duffy D, Smith C, Marshall V, Rupp R, Robson M. Amnion-derived cellular cytokine solution: a physiological combination of cytokines for wound healing. Eplasty 2008;8:157-165.

APPENDIX 1

SCHEDULE OF VISITS AND MEASUREMENTS

APPENDIX 2

EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

Visual Acuity Procedures (ETDRS Chart)

[redacted]

Equipment

[redacted]

Measurement Technique

[redacted]

[redacted]

[redacted]

[redacted]

LogMAR Visual Acuity Calculations

[redacted]

Slit Lamp Biomicroscopy Procedures

[redacted]

[redacted]

Intraocular Pressure

[redacted]

Dilated Fundoscopy

[redacted]

Ora Photography System

[redacted]

[redacted]

Capillary Tear Collection

[redacted]

Confocal Microscopy Procedures

[redacted]

Conjunctival Inflammation Scale

[redacted]

Ora proprietary scales – Not for distribution without permission

Allergen Challenge Scales

[redacted]

Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale

[redacted]

Ora Calibra™ Conjunctival Allergen Challenge Eyelid Swelling Scale

[redacted]

Ora Calibra™ Conjunctival Allergen Challenge Tearing/Watery Eyes Scale

[redacted]

Ora proprietary scales – Not for distribution without permission

Nasal Allergic Symptoms

Ora Calibra™ Rhinorrhea Scale

[redacted]

Ora Calibra™ Nasal Pruritus Scale

[redacted]

Ora Calibra™ Ear or Palate Pruritus Scale

[redacted]

Ora Calibra™ Nasal Congestion Scale

[redacted]

Ora Proprietary Scales – Not for distribution without permission

Investigator-Evaluated Signs (Ocular)

Ora Calibra™ Ocular Hyperemia Scale

[redacted]

Ora Calibra™ Chemosis Scale

[redacted]

Ora Proprietary Scales – Nor for distribution without permission

Subject-Reported Drop Comfort Scale

[redacted]

Ora Calibra™ Drop Comfort Questionnaire

[redacted]

APPENDIX 3

SAMPLE DOSING INSTRUCTIONS AND DIARY PAGE

Sample Dosing Diary Instructions:
Visits 3 to 4a Dosing Diary

DOSING INSTRUCTIONS

[redacted]

Sample Dosing Diary Instructions: Visits 3 to 4a Dosing Diary

GENERAL INSTRUCTIONS

Sample Dosing Diary Instructions: Visits 4b to 5a Dosing Diary

DOSING INSTRUCTIONS

Sample Dosing Diary Instructions:
Visits 4b to 5a Dosing Diary

GENERAL INSTRUCTIONS

Sample Daily Assessments Instructions:
Visits 4b to 5a Daily Assessments Diary

DIARY INSTRUCTIONS

- [redacted]
- [redacted]
- [redacted]
- [redacted].

Sample Dosing Diary Instructions: Visits 5b to 6 Dosing Diary

DOSING INSTRUCTIONS

Sample Dosing Diary Instructions:
Visits 5b to 6 Dosing Diary

GENERAL INSTRUCTIONS

[redacted]

\

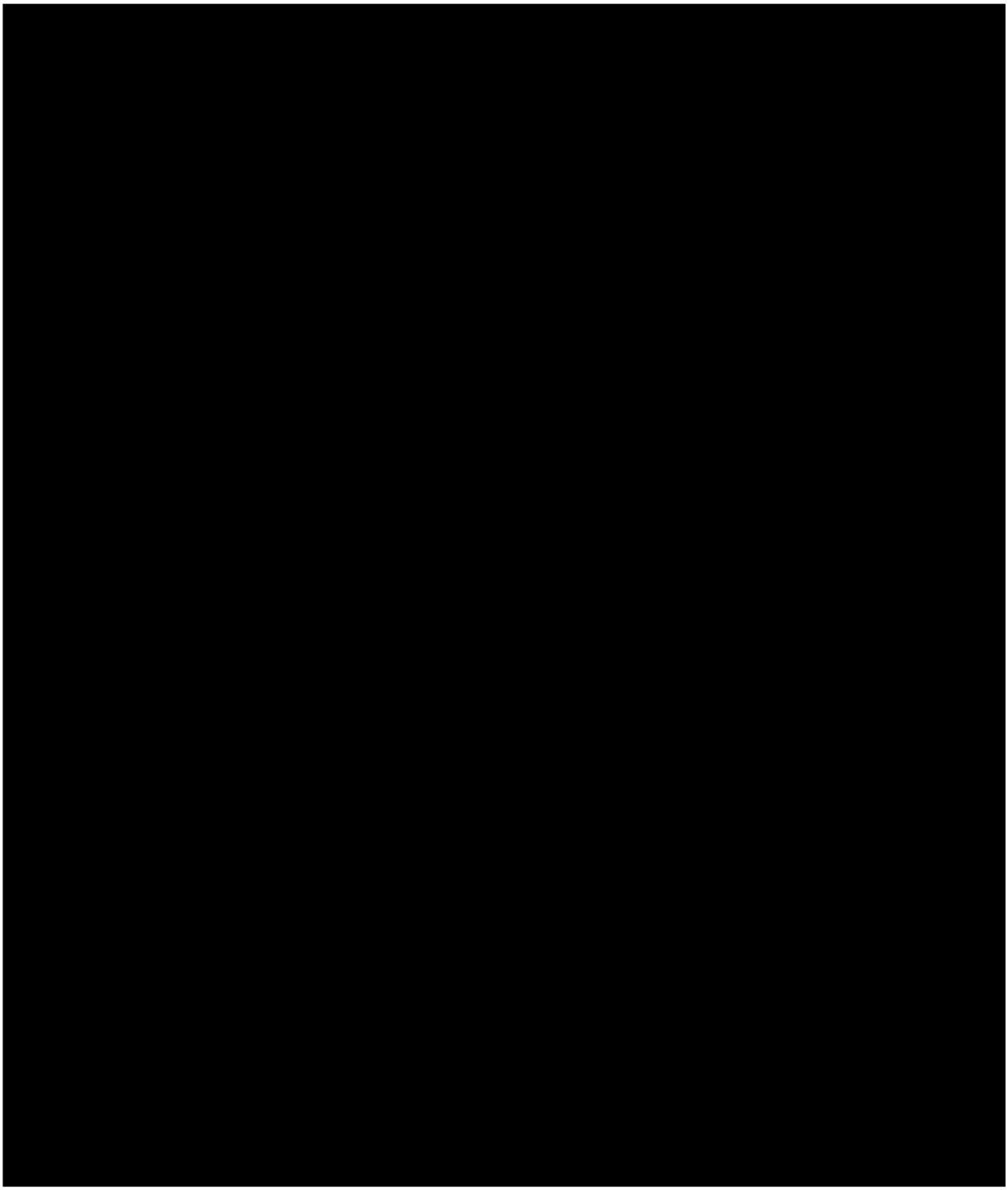
Sample Daily Assessments Instructions:
Visits 5b to 6 Daily Assessments Diary

DIARY INSTRUCTIONS

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

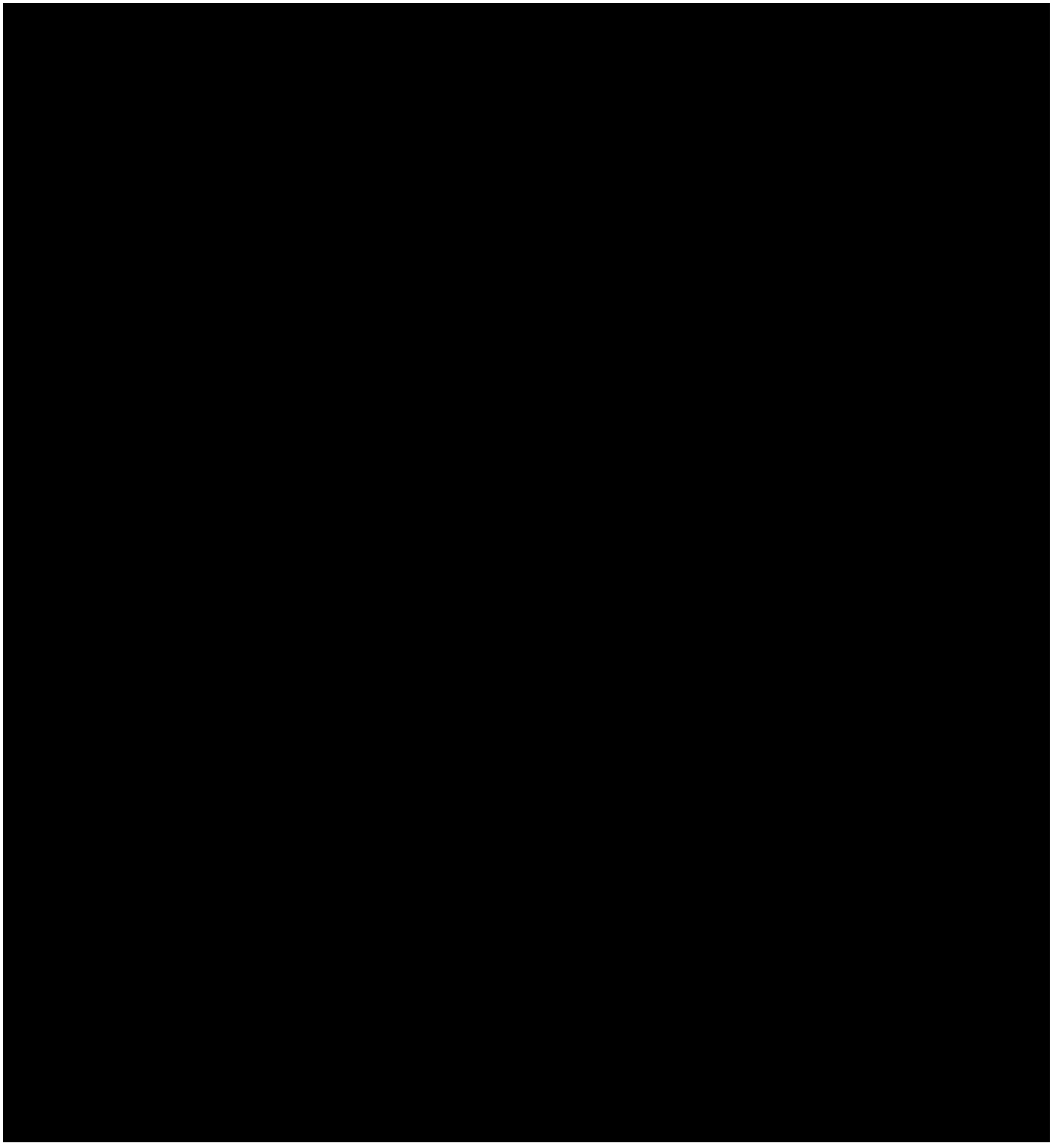
APPENDIX 4

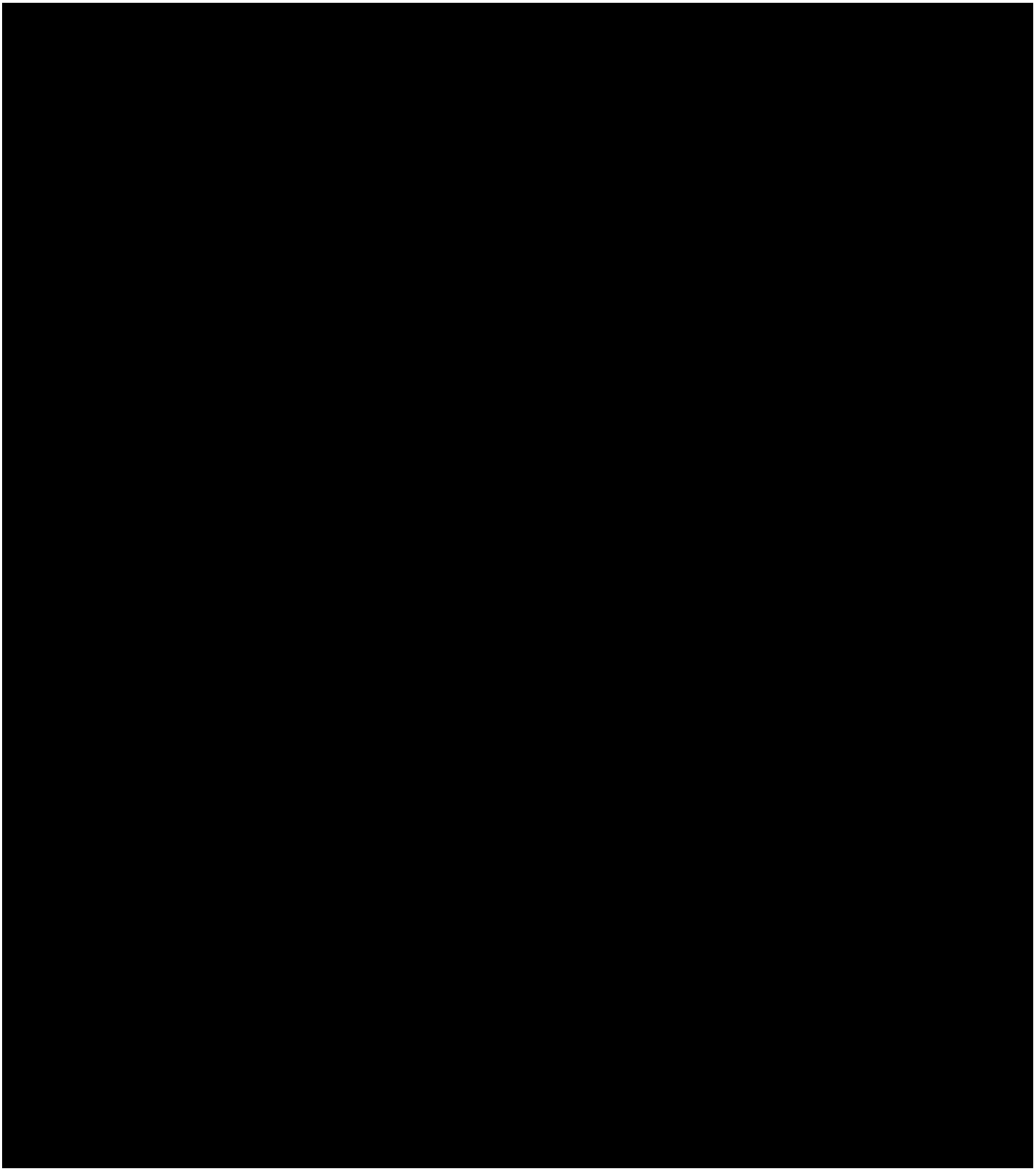
PACKAGE INSERT/ INVESTIGATIONAL PRODUCT COMPOSITION/ DESIGN (IF APPLICABLE)

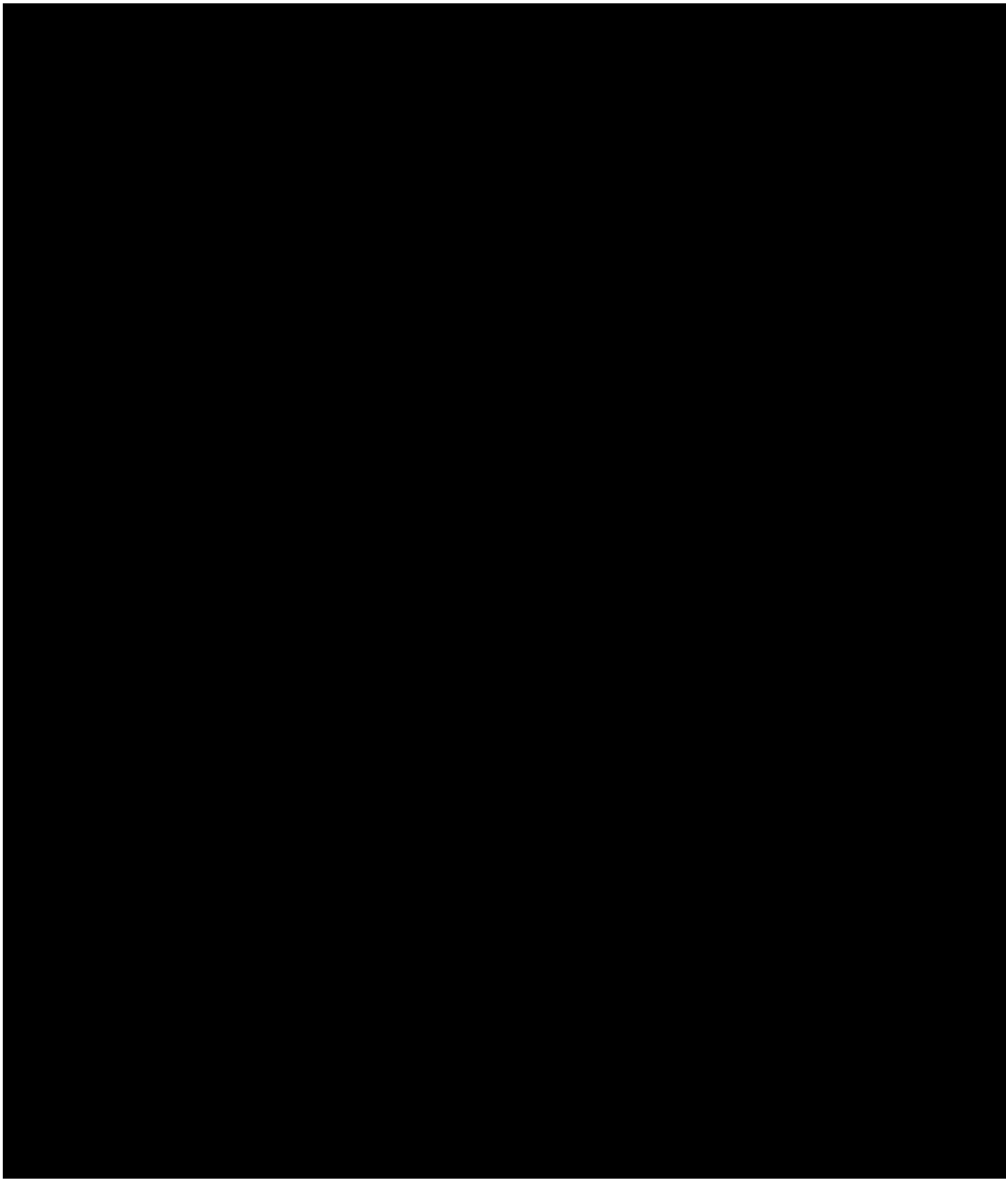


APPENDIX 5

PROTOCOL AMENDMENT SUMMARY







APPENDIX 6

SPONSOR APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo of ST266 for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	ST266-AC-201/16-100-0005
Final Date:	13 January 2017

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

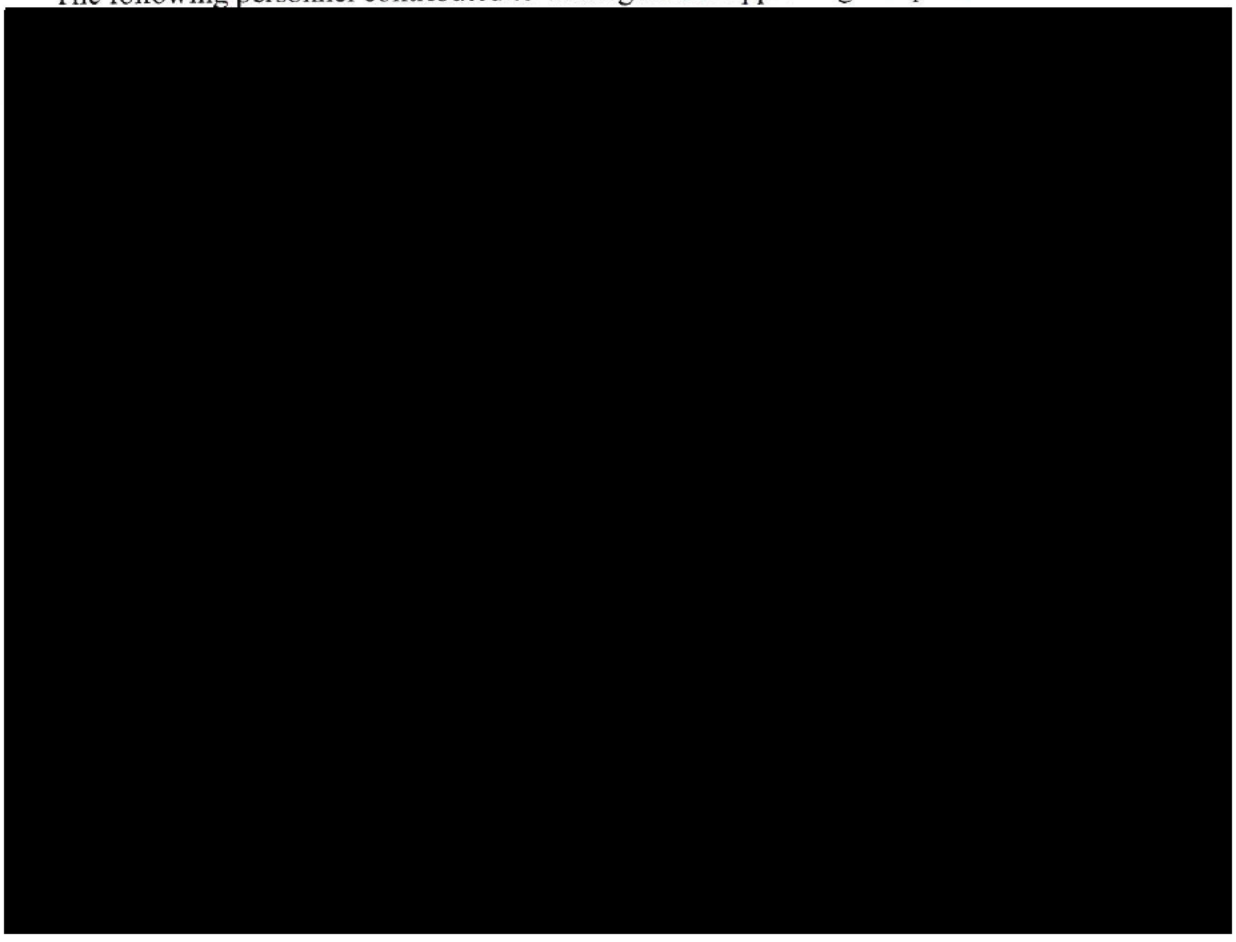
[redacted]

APPENDIX 7

ORA APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo of ST266 for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	ST266-AC-201/16-100-0005
Final Date:	13 January 2017

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



APPENDIX 7

ORA APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo of ST266 for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	ST266-AC-201/16-100-0005
Final Date:	13 January 2017

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

APPENDIX 8

INVESTIGATOR'S SIGNATURE

Protocol Title: A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo of ST266 for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: ST266-AC-201/16-100-0005

Final Date: 13 January 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>