1 CLINICAL TRIAL PROTOCOL: 17-100-0008

Protocol Title:	A Single-Center, Randomized, Double-Masked, Vehicle and Active-Controlled, Dose-Ranging Phase 2 Study Evaluating the Efficacy and Safety of PRT-2761 for the Treatment of Acute and Chronic Allergic Conjunctivitis Using the Conjunctival Allergen Challenge Model (Ora-CAC®)
Protocol Number:	17-100-0008
Name of Test Drug /Investigational Product:	PRT-2761 Ophthalmic Solution
IND/IDE/PMA Number:	130,141
Indication Studied:	Acute and chronic allergic conjunctivitis
Development Phase:	2
Brief Description:	This is a prospective, single-center, randomized, double-masked, vehicle and active-controlled, dose-ranging design study.
Name of Sponsor:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico, Suite C, #497 San Clemente, CA 92673 949-542-3882 www.alphairb.com
	Date
Original Protocol:	29-Aug-2017
Amendment 1.0 Date:	26-Sep-2017
Amendment 2.0 Date:	18-Oct-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

ORA PERSONNEL

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2 SYNOPSIS

Sponsor: Ora, Inc.

Name of Finished Product: PRT-2761 Ophthalmic Solution

Name of Active Ingredient: PRT-2761

Protocol Title: A Single-Center, Randomized, Double-Masked, Vehicle and Active-Controlled, Dose-Ranging Phase 2 Study Evaluating the Efficacy and Safety of PRT-2761 for the Treatment of Acute and Chronic Allergic Conjunctivitis Using the Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: 17-100-0008

Investigator: Single-Center

Study Phase of Development: 2

Objectives:

Primary Objective(s): To evaluate the efficacy and safety of two concentrations of PRT-2761 as a topical ophthalmic solution for the treatment of the signs and symptoms of acute and chronic allergic conjunctivitis.

Methodology:

Structure:

This is a prospective, single-center, randomized, double-masked, vehicle and active-controlled, dose-ranging design study.

Duration: 10 office visits over a period of up to 9 weeks

Screening Period: At Visit 1, subjects will sign the informed consent and an allergic skin test will be performed for subjects without documentation of a positive test within the past 24 months. At Visit 2, each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 3 using the same allergen they qualified with at Visit 2.

Treatment Period: Treatment will begin at Visit 4a after subjects are randomized. At this visit, subjects will receive an in-office dose of the treatment that they were randomized to receive. After this initial dose, subjects will receive 5 additional doses in-office at Visits 5a, 5b, 6a, 6b, and 7.

Summary of Visit Schedule:

Part 1: Acute Allergic Conjunctivitis

Visit 1 (Day -50 to Day -22): Screening / Informed Consent / Skin Test

Visit 2 (Day -21±3): Baseline Tear Collection of potential Confocal Micrsocopy Subjects / Titration CAC

Visit 3 (Day -14±3): Confirmation CAC / Confocal will be performed on a subset of up to 36 subjects. This subset of subjects will have tear collection performed prior to confocal microscopy and again at 2 hours (+1 hours) after instillation of the anesthetic used for confocal microscopy. Subjects will also be dispensed diaries for at home assessments of allergy.

Visit 4a (Day 1, Duration of Action Visit)*: Baseline Assessments, Randomization, in-office dose instillation with PRT-2761, PV or Patanol®.

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Visit 4b (Visit 4a+ 8 hrs [+1], Duration of Action Visit; CAC#1): CAC is performed 8 hours post Visit 4a dose, with post-CAC assessments of allergic signs and symptoms. Confocal will be performed on the same subset of subjects post all CAC assessments. This subset of individuals will also undergo tear collection prior to confocal.

Visit 5a (Day 15[±3] days), Onset of Action Visit; 2nd Dose/ CAC #2): In-office dose instillation with PRT-2761, PV or Patanol®. CAC is performed 15(+1) minutes post dose, with post-CAC assessments of allergic signs and symptoms.

Part 2: Chronic Allergic Conjunctivitis

Visit 5b (Visit 5a + 8 hrs [+1]; 3rd Dose/CAC #3)*: In-office dose instillation with PRT-2761, PV, Patanol®, or Pred forte® 8 hours from Visit 5a dose. CAC is performed 15(+1) minutes post dose, with post-CAC assessments of allergic signs and symptoms. The confocal subset of subjects will be dispensed cameras (Ora photography system) for at home assessments. All subjects will be dispensed diaries for at home assessments of allergy.

Visit 6a (Visit 5a + 24 hrs (±6 hrs) ; 4th Dose/CAC #4): In-office dose instillation with PRT-2761, PV, Patanol®, or Pred forte®. CAC is performed 15(+1) minutes post dose, with post-CAC assessments of allergic signs and symptoms.

Visit 6b (Visit 6a + 8 hrs [+1]; 5th Dose/CAC #5): In-office dose instillation with PRT-2761, PV, Patanol®, or Pred forte® 8 hours from Visit 6a dose. CAC is performed 15(+1) minutes post dose, with post-CAC assessments of allergic signs and symptoms. The confocal subset of subjects will also be dispensed cameras (Ora photography system) for at home assessments. All subjects will be dispensed diaries for at home assessments of allergy.

Visit 7 (6a + 24 hrs (±6 hrs); 6th Dose/CAC #6): In-office dose instillation with PRT-2761, PV, Patanol® or Pred forte®. CAC is performed 15(+1) minutes post dose, with post-CAC assessments of allergic signs and symptoms. Post all CAC assessments, the subset of subjects will undergo confocal microscopy and tear collection 2 hours (+1 hours) after instillation of the anesthetic used for confocal microscopy. Exit visit.

*15 of the subjects who were randomized to receive Patanol® at Visit 4a will continue to receive Patanol® at Visits 5a-7. The other 15 subjects who were randomized to receive Patanol® at Visit 4a will receive Patanol® at Visits 4a-5a and Pred forte® at Visits 5b-7.

Measures Taken to Reduce Bias:

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g. demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. In addition randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 3), by qualifying allergen type (seasonal and perennial) and by confocal participation (yes and no) to ensure balance for the primary endpoint of ocular itching. Finally, masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

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Study Population Characteristics

Number of Subjects:

Approximately 240 subjects will be screened to enroll 120 and complete 112.

Diagnosis

Acute and chronic allergic conjunctivitis

Inclusion Criteria

Subjects must:

1. be at least 18 years of age of either sex and any race;
2. provide written informed consent and sign the HIPAA form;
3. be willing and able to follow all instructions and attend all study visits;
4. (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening (must be negative) and at 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 initiation of the investigational product (IP) treatment (Visit 4a) and for one month after cessation of IP treatment. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. have a positive history of allergic conjunctivitis and a positive skin test reaction to a [redacted] allergen [redacted] Testing will be provided at Visit 1 if the subject has never been tested or if the skin test [redacted];
6. have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
7. have a positive bilateral CAC reaction[3] to allergen within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;
8. have a positive bilateral CAC reaction[5] to allergen for at least two out of the three time points following challenge at Visit 3;
9. be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6);
10. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study trial period.

Exclusion Criteria

Subjects may not:

1. have known contraindications or sensitivities to the use of any of the IP treatment or components.

[1] The subject must choose an acceptable method of birth control as specified in inclusion criterion d) 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.

[redacted]

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2. have any ocular condition in either eye 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, trichiasis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. have had ocular surgical intervention in either eye within three (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 in either eye;
5. have the presence of an active ocular infection in either eye (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 2** and during the study. Washout periods **prior to Visit 2** are as follows:

   7 Days:
   - systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine- vasoconstrictor drug combinations;
   - decongestants;
   - monoamine oxidase inhibitors;
   - all other topical ophthalmic preparations (including artificial tears);
   - lid scrubs;
   - prostaglandins or prostaglandin derivatives;
   - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

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

   45 Days:
   - depot-corticosteroids;

   2 Months:
   - immunosuppressive or cancer chemotherapeutic agents.

   **Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects at the end of Visit 2, Visit 3, Visit 4b, or Visit 7 after all evaluations are completed;*

7. have any significant illness [e.g., an autoimmune disease, severe cardiovascular disease (including arrhythmias)] the Investigator feels could expect to interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk. This includes but is not limited to: alcohol or drug abuse, poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, 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. [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 IP trial;
11. be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for at least 14 days prior to initiation of IP treatment and for one month after cessation of IP treatment, or has a positive urine

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pregnancy test at Visit 2;

12. have a history of ocular hypertension (OHT), glaucoma, or have an intraocular pressure (IOP) that is less than 8 millimeters Mercury (mmHg) or greater than 22 mmHg in either eye at Visit 2

Test Product, Dose and Mode of Administration, Batch Number: PRT-2761 0.5%, PRT-2761 1%

Subjects randomized to receive either concentration of PRT-2761 will be dosed with that concentration of PRT-2761 at Visit 4a and Visits 5a through 7 prior to CAC.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Vehicle (PV), Patanol®, Patanol®/Pred forte®

Subjects randomized to receive PV will be dosed with PV at Visit 4a and Visits 5a through 7 prior to CAC. Subjects randomized to receive Patanol® at Visit 4a will be further randomized into 2 groups: One group will receive Patanol® at Visit 4a and Visits 5a through 7. The other group will be dosed with Patanol® at Visits 4a and 5a and Pred forte® at Visits 5b through 7 prior to CAC.

Criteria for Evaluation:

Efficacy Measures:

Primary:

- Ocular itching evaluated by the subject at Visits 4b and 5a (for Duration and Onset of action, respectively) at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Conjunctival redness evaluated by the Investigator at Visits 4b and 5a (for Duration and Onset of action, respectively) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

Secondary:

- Ocular itching evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Conjunctival redness evaluated by the Investigator at Visits 5b, 6a, 6b, and 7 at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Episcleral and ciliary redness evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Chemosis evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Tearing evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)
- Eyelid swelling evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)
- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

Exploratory:

- Ocular itching evaluated by the subject at Visit 5b, 6a, 6b, and 7 at 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- Tearing evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)
- Eyelid swelling evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes

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post-CAC (0-3 scale, NOT allowing half-unit increments)

- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)Conjunctival, episcleral, and ciliary redness evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- Chemosis evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- In a subset of approximately 36 subjects who agree to undergo confocal microscopy, Conjunctival Inflammation as measured by confocal microscopy (0-4 scale, NOT allowing half-unit increments) at Visits 3, 4b, and 7. This number is estimated to be sufficient to ensure approximately 30 subjects in the confocal microscopy subset complete the trial.
- In this same subset of subjects who undergo confocal microscopy, tears will be collected from both eyes (prior to confocal microscopy) at Visit 3, 4a, 4b and 7. Tears will be analyzed for cytokine levels. At Visit 3, tear collection will be performed post-CAC.
- Diary assessments for subset of subjects undergoing confocal microscopy at Visits 3 and 4b. Additionally, all subjects will be dispensed diaries at Visits 5b and 6b. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening (all use a 0 to 4 scale, except eyelid swelling, 0 to 3).
- Digital photographs will be taken at-home of each eye (for subset of subjects undergoing confocal microscopy) prior to subjects completing diary assessments following Visits 5b and 6b.
- Digital photographs will be taken in-office of all subjects pre-CAC and within 30 minutes of the last post-CAC assessment at Visit 4b and Visit 5a.

Safety Measures:

- Slit Lamp Biomicroscopy
  The eyelids, conjunctiva, cornea, lens, and anterior chamber will be examined as part of the Slit Lamp Biomicroscopy exam.
- Dilated Ophthalmoscopy
  A dilated ophthalmoscopy will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology.
- Distance VA using an ETDRS chart
  A worsening of acuity of greater than 10 letters from Visit 2 will be considered an adverse event (AE)
- IOP
- AEs (reported, elicited, and observed)

Tolerability:

- Drop comfort assessment (0-10 unit scale) assessed by subject immediately upon instillation, at 30 seconds, and 1 minute post-instillation at Visit 4a
- Drop comfort descriptor questionnaire at 3 minutes post-instillation at Visit 4a

General Statistical Methods and Types of Analyses

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean,

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standard deviation (SD), median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages.

The efficacy analyses will be conducted in the intent-to-treat (ITT) population using the last observation carried forward method to handle missing and incomplete efficacy data. The ITT population is defined as all randomized subjects. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses. The average of each subject's eyes at each time point within each visit will be used for efficacy analyses. Sensitivity analysis on the primary endpoints will performed on the Per Protocol (PP) population defined as all subjects who complete the study through Visit 7 (Day 17) without major protocol violations. The PP population will be analyzed as treated using observed data only.

Safety analyses will be conducted in the safety population defined as all randomized subjects who have received treatments. The safety population will be analyzed as treated.

Primary Efficacy Analysis: The primary efficacy endpoints are ocular itching assessed at Visit 4b and 5a (Duration and Onset of Action, respectively) at 5(±1), 7(±1), 10(±1) minutes post-CAC (0-4 scale, allowing half unit increments) and conjunctival redness evaluated by the Investigator at Visit 4b and 5a (for Duration and Onset of action, respectively) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments). The average of each subject's eyes at each post-CAC time point will be used as the unit of analysis for both ocular itching and conjunctival redness. Ocular itching and conjunctival redness will each be analyzed using an analysis of covariance model for each post-CAC time point at these visits, with the time appropriate post-CAC scores at Visit 3 as a covariate and treatment group, including all four treatments, as the sole factor (least squared means will be used to compare each concentration of PRT-2761 to PV). Two-sample t-tests will be used as unadjusted sensitivity analyses at each post-CAC time point, as well as a non-parametric Wilcoxon rank sum tests (comparing each concentration of PRT-2761 to PV). At each post-CAC time point, treatment differences will be considered statistically significant for each primary endpoint if they are significant at a two-sided significance level of $\alpha = 0.05$.

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Secondary Efficacy Analysis: Continuous secondary endpoints will be analyzed using similar statistics methods to that of primary endpoints. Categorical endpoints will be analyzed using Pearson chi-squared statistic or Fisher's Exact test (if any expected cell count is <5). *Tolerability Analysis*: Drop comfort and drop descriptor assessments will be used to assess tolerability. Drop comfort will be summarized using number of observations, mean, median, standard deviation, minimum and maximum, and will be analyzed with two-sample t-tests. The drop descriptor assessment will be summarized using counts and percentages and will be analyzed using Fisher's exact or Chi-Square tests as appropriate.
Summary of Known and Potential Risks and Benefits to Human Subjects PRT-2761 has not been used in humans. In animal studies, it has been shown to be safe and well tolerated.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CRF	Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional/Independent Review Board
ITT	Intent To Treat
logMAR	Logarithm of the Minimum Angle of Resolution
mmHg	Millimeters of Mercury
NSAID	Nonsteroidal Anti-Inflammatory Drug
PV	Placebo Vehicle
Ora-CAC®	Ora Conjunctival Allergen Challenge (CAC)
PP	Per Protocol
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
VA	Visual Acuity

3 INTRODUCTION

Most approved treatments for ocular allergy are antihistamines, mast cell stabilizers, or both, and these drugs act primarily to reduce the signs and symptoms of the early phase allergic reaction. There is, however, evidence that suggests that many ocular allergy patients exhibit a persistent late phase reaction. The contribution of this underlying late-phase inflammatory response to the clinical signs and symptoms of chronic and/or severe ocular allergy requires that an anti-allergy product must be effective not only in the treatment of the acute allergic reaction, but also of the more complex chronic inflammatory environment that results from overlapping and continual allergen exposure.

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.[4]

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.[5] Following antigen exposure, conjunctival mast cells degranulate and release newly formed and pre-existing inflammatory mediators.[6] Histamine is the primary preformed mediator responsible for the typical early phase reaction that triggers itching, vasodilation and vascular leak leading to ocular redness, chemosis, and blepharitis. The early phase response occurs within minutes to hours following allergen exposure. Mast cells also synthesize and release cytokines, chemokines, and growth factors that initiate a cascade of inflammatory events leading to a late phase reaction characterized by recruitment of eosinophils, neutrophils, and subsequent lymphocytes and macrophages into the conjunctival tissues.[7,8]

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[4] Abelson, M. B., W. A. Chambers and L. M. Smith (1990). Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. Arch Ophthalmol 108(1): 84-88.

[5] Abelson, M. B., L. Smith and M. Chapin (2003). Ocular Allergic Disease: Mechanisms, Disease Sub-types, Treatment. The Ocular Surface 1(3): 38-60

[6] Ono, S. J. and M. B. Abelson (2005). Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 115(1): 118-122

[7] Bacon, A. S., P. Ahluwalia, A. M. Irani, L. B. Schwartz, S. T. Holgate, M. K. Church and J. I. McGill (2000). Tear and conjunctival changes during the allergen-induced early- and late-phase responses. J Allergy Clin Immunol 106(5): 948-954.

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. Following the CAC, the principal sign and symptom of acute allergic reaction, ocular itching and conjunctival redness, are typically monitored over time periods of 3-10 minutes and 7-20 minutes, respectively.

Modifying the conventional CAC model is useful for assessment of drug efficacy against more chronic states of inflammation than that observed after only one allergen challenge. The present protocol involves two parts: in the first part, the conventional method will be used in that duration and onset of action of PRT-2761 will be assessed after only one challenge. Subsequent to Visit 4a, four additional challenges will be conducted in subjects to mimic the chronic phase of ocular allergy. Subjects will enter a state of incrementally increasing allergic chronicity, and will be dosed prior to each of these challenges to assess drug onset of efficacy. This repeat-CAC model provides the opportunity to investigate the effects of the underlying inflammatory reaction on the ability of the tissues to mount a robust acute response to a subsequent allergen challenge. The repeat-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.

The Ora-CAC® model has been clinically validated and has been recognized by the US Food and Drug Administration (FDA) as a reliable method for evaluating novel ophthalmic pharmaceutical drugs.[9,10] 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.

4 STUDY OBJECTIVES

To evaluate the efficacy and safety of two concentrations of PRT-2761 as a topical ophthalmic solution for the treatment of the signs and symptoms of acute and chronic allergic conjunctivitis.

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

[9] Abelson, M. B., W. A. Chambers and L. M. Smith (1990). Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. Arch Ophthalmol 108(1): 84-88.

[10] Abelson, M. B. and O. Loeffler (2003a). Conjunctival allergen challenge: models in the investigation of ocular allergy. Curr Allergy Asthma Rep 3(4): 363-368.

5 CLINICAL HYPOTHESES

It is hypothesized that at least one concentration of PRT-2761 will be as safe as and more effective than vehicle treatment in the prevention of ocular itching and conjunctival redness associated with acute and/or chronic allergic conjunctivitis.

6 OVERALL STUDY DESIGN

This is a prospective, single-center, randomized, double-masked, vehicle and active-controlled, dose-ranging study to evaluate the efficacy and safety of PRT-2761 in two concentrations compared to Placebo Vehicle (PV), Patanol® and Patanol®/Pred forte® for the treatment of the signs and symptoms of chronic allergic conjunctivitis.

The trial will comprise of 10 office visits over a period of up to 9 weeks. Part 1 will be a conventional CAC protocol. Subjects who meet the entry criteria for itching and redness response to the CAC at Visits 2 and 3 will be randomized at Visit 4a (Day 1, Duration of Action Visit) in a 1:1:1:1 (PRT-2761 0.5%: PRT-2761 1%: PV:Patanol®) assignment ratio in the acute phase. Subjects randomized to the Patanol® treatment for the acute phase will further be randomized using a 1:1 (Patanol®: Pred forte®) assignment ratio for the chronic phase. After 8 hours, subjects will return for Visit 4b to be challenged with signs and symptoms assessed post-CAC. Subjects will return 14 days later for Visit 5a (Day 15, Onset of Action Visit), at which time they will be challenged 15 minutes after dosing with the same concentration of PRT-2761, PV, or Patanol® as randomized at Visit 4a. This will conclude Part 1 of the study.

Part 2 will be the assessment of chronic allergy and subjects will be challenged 15 minutes after dosing. If subjects were randomized to receive PRT-2761 0.5%, PRT-2761 1%, or PV at Visit 4a, subjects will continue to receive the same treatment at (Visits 5b, 6a, 6b and 7 at 8, 24, 32 and 48 hours from Visit 5a, respectively). Subjects who were randomized to receive Patanol® at Visit 4a will be further randomized into 2 groups. One group will continue to receive Patanol® through Visit 7. The other group will be dosed with Pred forte® at Visits 5b through 7. At Visit 7, final exit procedures will also be conducted and subjects will exit the study.

7 STUDY POPULATION

7.1 NUMBER OF SUBJECTS (APPROXIMATE)

Approximately 240 subjects will be screened to enroll 120 subjects and complete approximately 112 subjects.

Randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 3), by qualifying allergen type [redacted] and by confocal participation (yes and no).

7.2 STUDY POPULATION CHARACTERISTICS

Subjects of at least 18 years of age of either sex and any race, who meet all of the inclusion criteria and none of the exclusion criteria.

7.3 Inclusion Criteria

Subjects must:

1. be at least 18 years of age of either sex and any race;
2. provide written informed consent and sign the HIPAA form;
3. be willing and able to follow all instructions and attend all study visits;
4. (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit[11]; must not be lactating; and must agree to use a medically acceptable form of birth control[12] throughout the study duration and for at least 14 days prior to initiation of the investigational product (IP) treatment (Visit 4a) and for one month after cessation of IP treatment. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
5. have a positive history of allergic conjunctivitis and a positive skin test reaction to a [redacted] allergen [redacted]. Testing will be provided at Visit 1 if the subject has never been tested o[redacted]
6. have a calculated visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
7. have a positive bilateral CAC reaction[13] to allergen within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;
8. have a positive bilateral CAC reaction[15] to allergen for at least two out of the three time points following challenge at Visit 3;
9. be able and willing to avoid all disallowed medication for the appropriate washout period and during the study (see exclusion 6);
10. be able and willing to discontinue wearing contact lenses for at least 72 hours prior to Visit 2 and during the study trial period.

[11] The subject must choose an acceptable method of birth control as specified in inclusion criterion d) in order to continue in the study.
[12] 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.
[13] [redacted].

7.4 EXCLUSION CRITERIA

Subjects may not:

1. have known contraindications or sensitivities to the use of any of the IP treatment or components;
2. have any ocular condition in either eye 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, trichiasis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye);
3. have had ocular surgical intervention in either eye within three (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 in either eye;
5. have the presence of an active ocular infection in either eye (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 2** and during the study. Washout periods **prior to Visit 2** are as follows:

   7 Days:
   - systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine- vasoconstrictor drug combinations;
   - decongestants;
   - monoamine oxidase inhibitors;
   - all other topical ophthalmic preparations (including artificial tears);
   - lid scrubs;
   - prostaglandins or prostaglandin derivatives;
   - ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

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

   45 Days:
   - depot-corticosteroids;

   2 Months:
   - immunosuppressive or cancer chemotherapeutic agents.

   **Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects at the end of Visit 2, Visit 3, Visit 4b, or Visit 7, after all evaluations are completed;*

7. have any significant illness [e.g., an autoimmune disease, severe cardiovascular disease (including arrhythmias)] the Investigator feels could expect to interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk. This includes but is not limited to: alcohol or drug abuse,

poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, 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. [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 IP trial;
11. be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for at least 14 days prior to initiation of IP treatment and for one month after cessation of treatment, or has a positive urine pregnancy test at Visit 2;
12. have a history of ocular hypertension (OHT), glaucoma, or an intraocular pressure (IOP) that is less than 8 millimeters Mercury (mmHg) or greater than 22 mmHg in either eye at Visit 2.

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.

Sponsor and/or Investigator may discontinue any patient 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 Visits 4b and 5a (for Duration and Onset of action, respectively) at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

- Conjunctival redness evaluated by the Investigator at Visits 4b and 5a (for Duration and Onset of action, respectively) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

8.1.2 Secondary Efficacy Measure(s)

- Ocular itching evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

- Conjunctival redness evaluated by the Investigator at Visits 5b, 6a, 6b, and 7 at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments

- Episcleral and ciliary redness evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

- Chemosis evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

- Tearing evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

- Eyelid swelling evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)

- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

8.1.3 Criteria for Effectiveness

- To demonstrate efficacy for ocular itching, PRT-2761 in any concentration needs to show clinical superiority over PV by at least 0.5 units of a 5 point scale for all 3 post-CAC time points, 5(±1), 7(±1), 10(±1) minutes post-CAC and at least [redacted] of the post-CAC time points.

- To demonstrate efficacy for conjunctival redness, PRT-2761 in any concentration needs to show clinical superiority over PV by at least 0.5 units of a 5 point scale for all 3 post-CAC time points, 7(±1), 15(±1), 20(±1) minutes post-CAC [redacted] of the post-CAC time points.

- If ocular itching meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for ocular itching.

- If conjunctival redness meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for conjunctival redness.

- If both ocular itching and conjunctival redness meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for both ocular itching and conjunctival redness.

8.2 SAFETY MEASURES

- Slit Lamp Biomicroscopy

The eyelids, conjunctiva, cornea, lens, and anterior chamber will be examined as part of the Slit Lamp Biomicroscopy exam.

- Dilated Ophthalmoscopy
  Dilated ophthalmoscopy will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology.
- Distance VA using an ETDRS chart
  A worsening of acuity of greater than 10 letters from Visit 2 will be considered an adverse event (AE)
- IOP
- AEs (reported, elicited, and observed)

8.3 TOLERABILITY MEASURES

- Drop comfort assessment (0-10 unit scale) assessed by subject immediately upon instillation, at 30 seconds, and 1 minute post-instillation at Visit 4a
- Drop comfort descriptor questionnaire at 3 minutes post-instillation at Visit 4a

8.4 EXPLORATORY MEASURES

- Ocular itching evaluated by the subject at Visit 5b, 6a, 6b, and 7 at 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).

- Tearing evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

- Eyelid swelling evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)

- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

- Conjunctival, episcleral, and ciliary redness evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).

- Chemosis evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).

- In a subset of approximately 36 subjects who agree to undergo confocal microscopy, Conjunctival Inflammation as measured by confocal microscopy (0-4 scale, NOT allowing half-unit increments) at Visits 3, 4b, and 7. This number is estimated to be sufficient to ensure approximately 30 subjects in the confocal microscopy subset complete the trial.

- In this same subset of subjects who undergo confocal microscopy, tears will be collected from both eyes (prior to confocal microscopy) at Visit 3, 4a, 4b and 7. At Visit 3, tears will be collected both pre- and post-CAC. At Visit 4a tears will be collected prior to dosing. Tears will be analyzed for cytokine levels.
- Diary assessments for subset of subjects undergoing confocal microscopy at Visits 3 and 4b. Additionally, all subjects will be dispensed diaries at Visits 5b and 6b. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening (all use a 0 to 4 scale, except eyelid swelling, 0 to 3).
- Digital photographs will be taken at-home of each eye (for subset of subjects undergoing confocal microscopy) prior to subjects completing diary assessments following Visits 5b and 6b.
- Digital photographs will be taken in-office of all subjects pre-CAC and within 30 minutes of the last post-CAC assessment at Visit 4b and Visit 5a

9 STUDY MATERIALS

9.1 STUDY TREATMENT(S)

9.1.1 Study Treatment(s)/ Formulation(s)/ Medical Device Composition or Design

PRT-2761 will be assessed in two concentrations as an ophthalmic solution:

- Concentration 1: PRT-2761 0.5%, n = 30
- Concentration 2: PRT-2761 1%, n = 30

The following will be the Reference Therapy:

- PV (vehicle), n = 30
- Patanol® (active), n = 15
- Patanol® during acute phase/Pred forte® during chronic phase (active), n = 15

9.1.2 Instructions for Use and Administration

- At Visit 4a, a trained study technician will instill 1 drop of assigned investigational product into each eye.
- At Visit 5a, a trained study technician will instill the assigned investigational product in each eye and subjects will return 8 hours later for a second in-office dose that same day at Visit 5b.
- At Visit 6a, a trained study technician will instill the assigned investigational product in each eye approximately 24 hours from in-office dose at Visit 5a and subjects will return 8 hours later for a second in-office dose that same day at Visit 6b.
- At Visit 7, a trained study technician will instill the assigned investigational product in each eye 15 minutes prior to CAC.

The trained study technician instilling the investigational product will be considered unmasked since all bottles are not identical in appearance. This technician will not be

involved in any other procedures for this trial. During dosing, subjects will be called into a room out of view from other subjects and staff. Subjects will be instructed to look at the ceiling during instillation. The technician will instill the study medication in a manner which will minimize the chance of the subject seeing the bottle. All bottles will be kept out of direct view of the subjects.

9.2 OTHER STUDY SUPPLIES

Clarity HCG (RAC Medical Boca Raton, FL) will be used for pregnancy tests. Ora, Inc. will supply these pregnancy kits.

[redacted]

The ocular anesthetic agent (Fluress) and dilating drops used for the IOP and dilated ophthalmoscopy respectively will be supplied by Ora, Inc.

The ocular anesthetic agent (proparacaine hydrochloride ophthalmic solution) used for the confocal microscopy will be supplied by Ora, Inc.

10 STUDY METHODS AND PROCEDURES

10.1 SUBJECT ENTRY PROCEDURES

10.1.1 Overview

Subjects as defined by the criteria in Section 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 (ie, changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board. Failure to obtain a signed ICF renders the subject ineligible for the study. Subjects must be willing to return to the clinic for study Visits 1, 2, 3, 4a, 4b, 5a, 5b, 6a, 6b, and 7.

Prior to the completion of Visit 1 (Screening), if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process.

Subjects can be re-screened a maximum of two times.

10.1.3 Washout Intervals

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

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast-cell stabilizer drug combinations, H_1 antihistamine- vasoconstrictor drug combinations;
- decongestants;
- monoamine oxidase inhibitors;
- all other topical ophthalmic preparations (including artificial tears);
- lid scrubs;
- prostaglandins or prostaglandin derivatives;
- ocular, topical, or systemic NSAIDs;

14 Days

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

45 Days

- depot-corticosteroids;

2 Months

- immunosuppressive or cancer chemotherapeutic agents.

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 4a to be enrolled in the study.

10.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the study who sign an ICF will be assigned a 3-digit screening number that will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in sequential order beginning with 001. Randomization will be used to avoid bias in the assignment of subjects to treatment and time point, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups and across time points, and to enhance the validity of statistical comparisons.

Once a subject meets all qualification criteria at Visit 4a, they will be enrolled and randomly assigned to masked treatment using a 1:1:1:1 (PRT-2761 0.5%: PRT-2761 1%:PV:Patanol®) assignment ratio for the acute phase. Subjects randomized to the Patanol® treatment in the acute phase will further be randomized using a 1:1

(Patanol®:Pred forte®) assignment ratio for the chronic phase. Subjects will be randomized at Visit 4a (Day 1) by assignment of the lowest 4-digit randomization number available within the appropriate stratum. Randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 3), by qualifying allergen type (seasonal and perennial) and by confocal participation (yes and no) to ensure balance for the primary endpoint of ocular itching. The randomization numbers will start from x001, where x refers to the subject's stratum as follows:

[redacted]

The first 36 subjects who qualify after post-CAC assessments at Visit 3 and had tear collection at Visit 2, will be in the confocal microscopy subset. This number is estimated to ensure approximately 30 subjects in the confocal microscopy subset complete the trial. At Visit 4, these individuals will be assigned to a kit number from Stratum 5, 6, 7, or 8.

Once 36 subjects have completed confocal microscopy at Visit 3, any subjects who had tear collection at Visit 2, will not have additional tear collections or confocal microscopy. At Visit 4, these individuals will be assigned to a kit number from Stratum 1, 2, 3, or 4.

No randomization numbers will be skipped or omitted.

At Visit 4a, if a subject requires a kit from their assigned stratum, based on the above criteria, and there are no longer any kits available for that stratum, the subject will be not be randomized and will be deemed a screen failure.

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

Refer to Section 10 for a complete list of washout periods for the following prohibited medications and treatments:

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

If a subject uses a disallowed medication, this will be recorded as a protocol violation. Protocol violations must be reported to the IRB in accordance with their standard operating procedures.

10.2.2 Escape Medications

Cold compresses should first be used in the management of allergic symptoms. Subjects may be prescribed anti-inflammatory or anti-allergy medication at the Investigator's discretion. Subjects 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 Visit 2, Visit 3, Visit 4b, or Visit 7, after all evaluations are completed.

10.2.3 Special Diet or Activities

Not Applicable.

10.3 EXAMINATION PROCEDURES

The following procedures will be conducted at one or more visits, as listed below.

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

10.3.1.1 VISIT 1 (Day -50 to -22): Screening / Informed Consent / Skin Test

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

  Prior to the completion of Visit 1 (Screening), if it is determined a subject did not in fact meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process.

  Subjects can be re-screened a maximum of two times.

- *Allergic Skin Test:* A diagnostic test for allergic disease (skin test) will be performed for subjects without documentation of a positive test within the past 24 months.
- *Demographic data and medical/medication/ocular and non-ocular history:* Collect and record all demographic data, medical history, any medications, and any underlying condition(s). Current underlying conditions, including those that began within the last thirty days, which may have been resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 45 days prior to screening.
- *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).
- *Adverse Event Query:* Adverse Events/Adverse Device Effects (both elicited and observed; expected and unexpected; suspected relationship to the treatment, suspected unrelated, and not related) will be monitored throughout the study. All adverse events (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness.
- *Scheduling of Next Visit (Visit 2)*

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

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Urine Pregnancy Test (for females of childbearing potential):* Women 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.

- *Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score of 0.7 logMAR or better in each eye in order to qualify.
- *Initial Ocular and Nasal Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy:* A slit-lamp examination will be performed in both eyes to exclude subjects with disallowed ocular conditions. Findings of abnormality which are not exclusionary should be recorded as Medical History.
- *Tear Collection:* Tears will be collected from up to 60 subjects to ensure there are enough potential subjects at Visit 3 for the confocal microscopy subset. If 5µl of tears is not collected at Visit 2, the subject will not have any additional tears collected for this trial and will not be a member of the confocal subset. The technician collecting tears will note the subject's reflex tearing, if applicable (see **Appendix 2**). There will be at least a 30 minute wait period between Tear Collection and the Titration CAC.

- *Review of Inclusion/Exclusion Criteria:* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.
- *Titration Conjunctival Allergen Challenge (CAC):* A[redacted]
  - [redacted]
  - [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Upon completion of the initial titration CAC, subjects will receive an ocular examination by the Investigator to evaluate all Investigator-evaluated efficacy measures and confirm

the subject's qualification. Subjects will be asked to assess their ocular and nasal symptoms.

- *IOP Measurement:* Intraocular Pressure (IOP) will be measured in each eye by contact tonometry, for qualified subjects.
- *Dilated Ophthalmoscopy:* A dilated ophthalmoscopy will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology, for qualified subjects.
- *Review of Inclusion/Exclusion Criteria*
- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.
- *Adverse Event Query*
- *Scheduling of Next Visit (Visit 3)*

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

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy*
- *Digital Imaging:* Digital photographs may be taken of each eye.
- *Review of Inclusion/Exclusion Criteria*
- *Confirmation CAC:* [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7 (±1), and 10(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-challenge and assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), and 20(±1) minutes post-challenge (**Appendix 2**). If the subject fails

to react positively [redacted] in both eyes in at least two (2) out of the first three (3) time points[14], he/she will be excluded from the study.

Digital Imaging: Digital photographs may be taken of each eye within 30 minutes of the last post-CAC assessment.

- *Tear Collection:* Tears will be collected from the subset of subjects (approximately 36) that agree to receive confocal microscopy. 5µL of tears will be collected from each eye prior to confocal microscopy procedures. If 5µl of tears is not collected at Visit 3 post-CAC, the subject will remain in the confocal microscopy subset but no further tear collections will be performed. The technician collecting tears will note the subject's reflex tearing, if applicable (see **Appendix 2**).
- *Confocal Microscopy:* The first 36 subjects who qualify after post-CAC assessments, and had tears successfully collected at Visit 2, will be in the confocal subset to ensure that approximately 30 subjects complete the trial. Confocal microscopy of the left eye will be performed following tear collection.
- *Diary Dispensation:* The subset of subjects undergoing tear collection and confocal microscopy will be dispensed a diary to complete daily assessments prior to bedtime on the evening of Visit 3 and upon awakening the next morning. Subjects will be given a mailing label and instructed to mail the diary back to the site following their morning assessments.
- *Tear Collection:* Tears (5µL from each eye) will be collected from the confocal subset at 2 (+1) hours after instillation of the anesthetic used for confocal microscopy procedures. If 5µl of tears from each eye is not collected, the subject will remain in the confocal microscopy subset but no further tear collections will be performed. The technician collecting tears will note the subject's reflex tearing, if applicable (see **Appendix 2**).
- *Review of Inclusion/Exclusion Criteria*
- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.
- *Adverse Event Query*
- *Schedule (Visit 4a):* Subjects will be asked to return to the office 7 days later for Visit 4a, the Duration of Action Visit.

[14] Not necessarily at the same time point

10.3.1.4 VISIT 4a (Day 1): 1st Dose, Enrollment / Randomization to PRT-2761, PV or Patanol® & in-office instillation

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Assessments Diary Review and Collection:* Diary will be collected (if not mailed in) and reviewed.
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy*
- *Review Inclusion and Exclusion Criteria*
- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria and qualify to continue in the study will be randomly assigned to masked treatment using a 1:1:1:1 (PRT-2761 0.5%: PRT-2761 1%: PV: Patanol®) assignment ratio for the acute phase. Subjects randomized to the Patanol® treatment in the acute phase will further be randomized using a 1:1 (Patanol®: Pred forte®) assignment ratio for the chronic phase. Subjects will be randomized by assignment of the lowest randomization number available within the appropriate stratum. Randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 3), by qualifying allergen type (seasonal and perennial), and by confocal participation (yes and no) to ensure balance for the primary endpoint of ocular itching. No numbers will be skipped or omitted. If a subject requires a kit from their assigned stratum, based on the above criteria, and there are no longer any kits available for that stratum, the subject will be not be randomized and will be deemed a screen failure.
- *Investigational Product Instillation:* A[redacted]
- *Drop Comfort Assessment:* Drop comfort will be assessed immediately upon instillation, at 30 seconds, and 1 minute post-instillation (0 – 10 scale).
- *Drop Comfort Descriptor Questionnaire:* The subject will select 3 descriptor terms for drop comfort at 3 minutes post-instillation.
- *Adverse Event Query*

- *Scheduling of Next Visit (Visit 4b):* Subjects will be asked to return to the office 7.5 hours later for Visit 4b, the Duration of Action CAC Visit.

10.3.1.5 VISIT 4b (8 [+1] Hours Post-Dose): Duration of Action, CAC #1

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* [redacted]
- *Slit Lamp Biomicroscopy*
- *Digital Imaging:* Digital photographs may be taken of each eye.
- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), and 10(±1) minutes 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 7(±1), 15(±1) and 20(±1) minutes post-challenge (**Appendix 2**).
- *Digital Imaging:* Digital photographs may be taken of each eye within 30 minutes of the last post-CAC assessment.
- *Tear Collection:* Tears will be collected from the subset of subjects (up to 36) that agree to receive confocal microscopy. 5µL of tears will be collected from each eye prior to confocal microscopy procedures. If 5µl of tears is not collected at Visit 4b post-CAC, the subject will remain in the confocal microscopy subset but no further tear collections will be performed. The technician collecting tears will note the subject's reflex tearing, if applicable (see **Appendix 2**).
- *Confocal Microscopy:* Following digital photographs, the same subset of subjects that underwent confocal at Visit 3 will undergo confocal microscopy of the left eye.
- *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*

- *Scheduling for Next Visit (Visit 5a):* Subjects will be asked to return to the office 14 days later for Visit 5a, the Onset of Action CAC Visit.

10.3.1.6 VISIT 5a (Day 15±3): Onset of Action Visit, 2nd Dose/CAC #2

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Digital Imaging:* Digital photographs may be taken of each eye.
- *Investigational Product Instillation:* A [redacted].
- *Conjunctival Allergen Challenge (CAC)*: [redacted].
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), and 10(±1) minutes 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 7(±1), 15(±1) and 20(±1) minutes post-challenge (**Appendix 2**).
- *Digital Imaging:* Digital photographs may be taken of each eye within 30 minutes of the last post-CAC assessment.
- *Adverse Event Query*
- *Scheduling for Next Visit, 8 hours later (Visit 5b):* Subjects will be asked to return to the office 7.5 hours later for Visit 5b, start of Part 2, Chronic Ocular Allergy Visits.

10.3.1.7 VISIT 5b (8 [+1] Hours Post-Dose at Visit 5a) 3rd Dose/CAC #3

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*

- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation:* A[redacted]
- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), 10(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-challenge. Assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes post-challenge (**Appendix 2**).
- *Diary Dispensation:* All subjects will be dispensed a diary to complete daily assessments prior to bedtime and upon awakening beginning the evening of Visit 5b. Subjects will be instructed to bring the diary to the next visit (Visit 6a) for a compliance check.
- *Ora Photography System:* The subset of subjects who underwent confocal microscopy will be dispensed cameras for at home assessments, to be done alongside diary assessments.
- *Adverse Event Query*
- *Scheduling for Next Visit (Visit 6a):* Subjects will be asked to return to the office the following day (Day 16), approximately 24 hours from Visit 5a.

10.3.1.8 VISIT 6a (24 hours (±6 hrs) Post-Dose at Visit 5a): 4th Dose/CAC #4

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Assessments Diary Review and Collection*: Assessments diary will be collected and reviewed for compliance from Visit 5b to Visit 6a and to address any queries.
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation:* [redacted]

[redacted]

- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), 10(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-challenge. Assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes post-challenge (**Appendix 2**).
- *Adverse Event Query*
- *Scheduling of Next Visit (Visit 6b):* Subjects will be asked to return to the office 7.5 hours later for visit 6b.

10.3.1.9 VISIT 6b (8 [+1] Hours post-Visit 6a,): 5th Dose/CAC #5

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Investigational Product Instillation:* [redacted]
- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), 10(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-challenge. Assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes post-challenge (**Appendix 2**).

- *Diary Dispensation:* All subjects will be dispensed a diary to complete daily assessments prior to bedtime and upon awakening until the morning of Visit 7. Subjects will be instructed to bring the diary to the next visit (Visit 7) for a compliance check.
- *Ora Photography System:* The subset of subjects who underwent confocal microscopy will be dispensed cameras for at home assessments, to be done alongside diary assessments.
- *Adverse Event Query*
- *Scheduling of next visit (Visit 7):* Subjects will be asked to return to the office the following day (Day 17) Visit 7.

10.3.1.10 Visit 7(24 hours (±6 hrs) Post-Dose at Visit 6a): 6th Dose/CAC #6

- *Update of Medical/Medication History*
- *Adverse Event Query*
- *Assessments Diary Review and Collection*: Assessments diary will be collected and reviewed for compliance from Visit 6b to Visit 7 and to address any queries.
- *Urine Pregnancy Testing:* This will be given to all women of childbearing potential
- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Pre-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment*
- *Slit Lamp Biomicroscopy*
- *Digital Imaging:* Digital photographs may be taken of each eye.
- *Investigational Product Instillation:* [redacted]
- *Conjunctival Allergen Challenge (CAC)*: [redacted]
- *Post-CAC Ocular and Nasal Allergic Signs and Symptoms Assessment:* Assessment of itching will be made by the subject at 5(±1), 7(±1), 10(±1), 15(±1), 20(±1), 25(±1), and 30(±1) minutes following allergen challenge. Assessments of redness and chemosis will be graded by the Investigator at 7(±1), 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-challenge. Assessments of eyelid swelling, tearing/watery eyes, and nasal symptoms will be made by the subject at 7(±1), 15(±1) and 20(±1) minutes post-challenge (**Appendix 2**).

- *Visual Acuity Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 2 will be considered an adverse event.
- *Slit Lamp Biomicroscopy*
- *Digital Imaging:* Digital photographs may be taken of each eye within 30 minutes of the last post-CAC assessment.
- *Confocal Microscopy:* Following digital photographs, the same subset of subjects that underwent confocal at Visit 3 will undergo confocal microscopy of the left eye.
- *Tear Collection:* Tears (5µL from each eye) will be collected from the confocal subset 2 hours (+1 hours) after instillation of the anesthetic used for confocal microscopy procedures. The technician collecting tears will note the subject's reflex tearing, if applicable (see **Appendix 2**).
- *IOP Measurement:* Intraocular Pressure (IOP) will be measured in each eye by contact tonometry.
- *Dilated Ophthalmoscopy:* A dilated ophthalmoscopy will be performed by the Investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology.
- *Relief Drop Instillation:* Subjects may receive a dose of a currently marketed, topical ophthalmic anti-allergic agent (i.e., anti-histamine/vasoconstrictor combination products like Visine®-A®) as they leave the office to relieve any immediate discomfort caused by the allergic reaction.
- *Adverse Event Query*
- *Study Exit*

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.

10.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

10.4.1 Scheduled Visits

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

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

10.4.2 Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

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

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit), include:

- Update of Medical/Medication History
- Assessment of AEs
- Visual Acuity Using an ETDRS chart
- Pregnancy Testing
- Slit Lamp Examination
- Digital Imaging
- IOP Measurement
- Dilated Ophthalmoscopy Examination

10.5 COMPLIANCE WITH PROTOCOL

Site staff will review concomitant medication use at each visit.

If at any point during treatment the subject is experiencing discomfort or an undesirable reaction due to PRT-2761, PV, Patanol®, or Pred forte®, drug should be discontinued and the subject will exit the study.

Subjects who are inappropriately enrolled will 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 CRF.

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)
- manifest clinically active signs and symptoms of allergic conjunctivitis during the ocular and nasal allergic signs and symptoms assessment at Visit 5a [redacted]
- 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 will be clearly documented on the eCRF.

10.7 STUDY TERMINATION

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

10.8 STUDY DURATION

10 office visits over a period of up to 9 weeks.

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 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. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (eg, anatomical limitations), and therapeutic parameters (eg, energy applied, sizing, dose release) associated with medical device.

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 CRF. 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 1 comprehensive event.

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

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 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.

11.2 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 cab 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.

11.3 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.

AEs that are mentioned in the IB or ROPI as occurring with a class of products or as anticipated from the pharmacological/ mechanical (or other) properties of the product, but

are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

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

11.4 SERIOUS ADVERSE EVENTS

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

- Death;
- A life-threatening AE;

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

- Inpatient hospitalization or prolongation of existing hospitalization;

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

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

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

  Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (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.

11.5 PROCEDURES FOR REPORTING ADVERSE EVENTS

All AEs and their outcomes must be reported to Ora 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.

11.5.1 Reporting a Suspected Unexpected Adverse Reaction

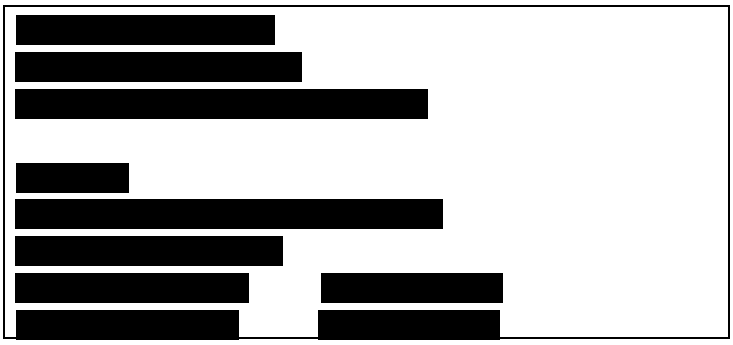
All AEs that are 'suspected' and 'unexpected' are to be reported to Ora and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

11.5.2 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 case report forms. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the case report form. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora 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 with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs and ADEs:



11.6 PROCEDURES FOR UNMASKING (IF APPLICABLE)

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. The Investigator will contact Ora with the details of the emergency unmasking request. Ora will make the final determination if the unmasking request will be granted. If granted, the Investigator will be permitted to use the code-break instructions available on site.

Each kit will be labeled with a two panel scratch off label. The right panel of the label, containing the scratch off portion, should be placed in the corresponding subject binder. If the Investigator determines that emergency unmasking is necessary, the Investigator should locate the subject binder containing the label and scratch off the laminate section to reveal the assigned treatment. The Investigator must also indicate in source documents and in the CRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

Subjects will have the IP treatment discontinued immediately if treatment assignment is unmasked.

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

AEs will be followed until:

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

If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious adverse events identified on the last scheduled contact must be recorded on the AE CRF with the status noted.

12 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

12.1 INTENT-TO-TREAT POPULATION

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

12.2 PER PROTOCOL POPULATION

The Per Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 5a (Day 15) with no major protocol violations. This population will be analyzed as treated using observed data only for confirmatory analyses.

12.3 SAFETY POPULATION

The safety population includes all randomized subjects who received at least one dose of investigational treatment. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

12.4 GENERAL IMPUTATION METHODS

[redacted]

12.5 PRIMARY EFFICACY ENDPOINTS

The primary efficacy endpoints are:

- Ocular itching evaluated by the subject at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) at Visits 4b and 5a.
- Conjunctival redness evaluated by the Investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) at Visits 4b and 5a.

12.6 CRITERIA FOR EFFICACY

To demonstrate efficacy for ocular itching, PRT-2761 in any concentration needs to show clinical superiority over PV [redacted] s, 5(±1), 7(±1), 10(±1) minutes post-CAC [redacted] of the post-CAC time points.

To demonstrate efficacy for conjunctival redness, PRT-2761 in any concentration needs to show clinical superiority over PV [redacted] 7(±1), 15(±1), 20(±1) minutes post-CAC [redacted] of the post-CAC time points.

If ocular itching meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for ocular itching.

If conjunctival redness meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for conjunctival redness.

If both ocular itching and conjunctival redness meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for both ocular itching and conjunctival redness.

12.7 SECONDARY EFFICACY ENDPOINTS

Secondary efficacy endpoints include the following:

- Ocular Itching at 5(±1), 7(±1) and 10(±1) minutes post-CAC evaluated by the subject (0-4 scale, allowing half-unit increments) at Visits 5b, 6a, 6b and 7
- Conjunctival Redness at 7(±1), 15(±1), and 20(±1) minutes post-CAC evaluated by the Investigator (0-4 scale, allowing half-unit increments) at Visits 5b, 6a, 6b and 7
- Ciliary and episcleral redness at 7(±1), 15(±1), and 20(±1) minutes post-CAC evaluated by the Investigator (0-4 scale, allowing half-unit increments) at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7)
- Chemosis evaluated at 7(±1), 15(±1), and 20(±1) minutes post-CAC by the Investigator (0-4 scale, allowing half-unit increments) at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7)
- Eyelid swelling evaluated at 7(±1), 15(±1), and 20(±1) minutes post-CAC by the subject (0-3 scale, NOT allowing half-unit increments) at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7)
- Tearing/watery eyes evaluated at 7(±1), 15(±1), and 20(±1) minutes post-CAC by the subject (0-4 scale, NOT allowing half unit increments) at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated at 7(±1), 15(±1), and 20(±1) minutes post-CAC by the subject (0-4 scale, NOT allowing half-unit increments) at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7)

12.8 STATISTICAL HYPOTHESES

[redacted]

[redacted]

[redacted]

[redacted]

12.9 SAMPLE SIZE

[redacted]

12.10 DEMOGRAPHIC AND BASELINE MEDICAL HISTORY

The demographic and baseline medical history data will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, SD, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

12.11 PRIMARY EFFICACY ANALYSES

The primary efficacy endpoints are ocular itching assessed at 5(±1), 7(±1), 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) and conjunctival redness evaluated by the Investigator at 7(±1), 15(±1), 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) at Visit 4b (Duration of Action Visit) and 5a (Onset of Action Visit). The average of each subject's eyes at each post-CAC time point will be used as the unit of analysis for both ocular itching and conjunctival redness. Ocular itching and conjunctival redness will each be analyzed using an analysis of covariance (ANCOVA) model for each post-CAC time point at each visit, with the time appropriate post-CAC scores at Visit 3 as a covariate and treatment group (including all four treatments: PRT-2761 0.5%, PRT-2761 1%, PV, Patanol®), as the sole factor. Least square (LS) means will be used to compare each concentration of PRT-2761 to PV. Two-sample t-tests will be used as unadjusted sensitivity analyses at each post-CAC time point, as well as a non-parametric Wilcoxon rank sum tests (comparing each concentration of PRT-2761 to PV). At each post-CAC time point, treatment differences

[redacted]

Treatment success is defined as PRT-2761, for at least one concentration, showing clinical superiority over PV [redacted] 5(±1), 7(±1), 10(±1) minutes post-CAC for ocular itching and 7(±1), 15(±1), 20(±1) minutes post-CAC for conjunctival redness, a[redacted] of the post-CAC time points measured for both ocular itching and conjunctival redness.

The primary efficacy analyses will be conducted on the ITT population using the last observation carried forward method for missing data as described in Section 12.4. Sensitivity or supportive analyses will be performed on the ITT population using observed data only, [redacted]

12.12 SECONDARY EFFICACY ANALYSIS

Analyses will be performed on quantitative secondary endpoints in a manner similar to primary endpoints. Qualitative measures will be analyzed using Fisher's exact test or Chi-Square test as appropriate (comparing PRT-2761 to PV). Secondary endpoints include ocular itching (at Visits 5b, 6a, 6b, 7), conjunctival redness (at Visits 5b, 6a, 6b, 7), episcleral and ciliary redness, chemosis, eyelid swelling, tearing/watery eyes, rhinorrhea, nasal pruritus, ear or palate pruritus, nasal congestion (at Visits (4b, 5a, 5b, 6a, 6b, 7). The secondary endpoints will be analyzed for the ITT population with observed data only and for the PP population with observed data only. The exploratory measure, conjunctival inflammation, at Visits 3, 4b, and 7, will be analyzed as described above.

[redacted]

Additionally, similar analyses will be completed on all efficacy endpoints secondarily to compare each concentration of PRT-2761 to Patanol® [acute and chronic phase] and Pred forte® [chronic phase].

12.13 ADJUSTMENT FOR MULTIPLICITY

[redacted]

[redacted]

[redacted].

12.14 SAFETY ANALYSIS

The primary safety variable is the incidence of subjects with any AE during the entire study. The percentage of subjects with specific treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. Incidence will be tabulated by Medical Dictionary for Regulatory Activities System Organ Class and preferred term within each system organ class. The secondary safety variables of slit lamp biomicroscopy, dilated fundoscopy, VA, and IOP will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

12.15 TOLERABILITY MEASURES

Drop comfort and drop descriptor assessments will be used to assess tolerability. Drop comfort will be summarized using number of observations, mean, median, standard deviation, minimum and maximum, and will be analyzed with two-sample t-tests. The drop descriptor assessment will be summarized using counts and percentages and will be analyzed using Fisher's exact or Chi-Square tests as appropriate.

12.16 SUBGROUP ANALYSIS

No subgroup analyses are planned.

12.17 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.

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

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 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.

13.4.2 Photography and Videos

Photographs and/or videos may be taken of each subject's eyes prior to CAC and/or instillation of investigational product and/or post-CAC (prior to confocal microscopy) at Visits 3, 4b, 7, and early exit/unscheduled visit.

Digital photographs may also be taken at home by the subset of subjects undergoing confocal after Visit 5b and 6b.

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

13.5.1 Labeling/Packaging

Investigational product will be packaged into clinical kits. Each kit will be labeled with the study information on a double panel, scratch off label and the kit will contain two bottles of investigational product. Each bottle will be labeled with a kit number and visit number range (4a-5a and 5b-7).

All clinical labels will meet applicable regulatory requirements. Investigational product will be packaged and labeled based on the randomization schedule generated prior to the start of the study.

13.5.2 Storage of Investigational Product

The study drugs must be stored in a secure area accessible only to the investigator and his/her designees. Study drug(s) must be kept at room temperature (15-25°C), and secured at the investigational site in a locked container.

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

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora

and the study sponsor will have the final decision regarding the manuscript and publication.

14 REFERENCES

See footnotes throughout this document.

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

[redacted]

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

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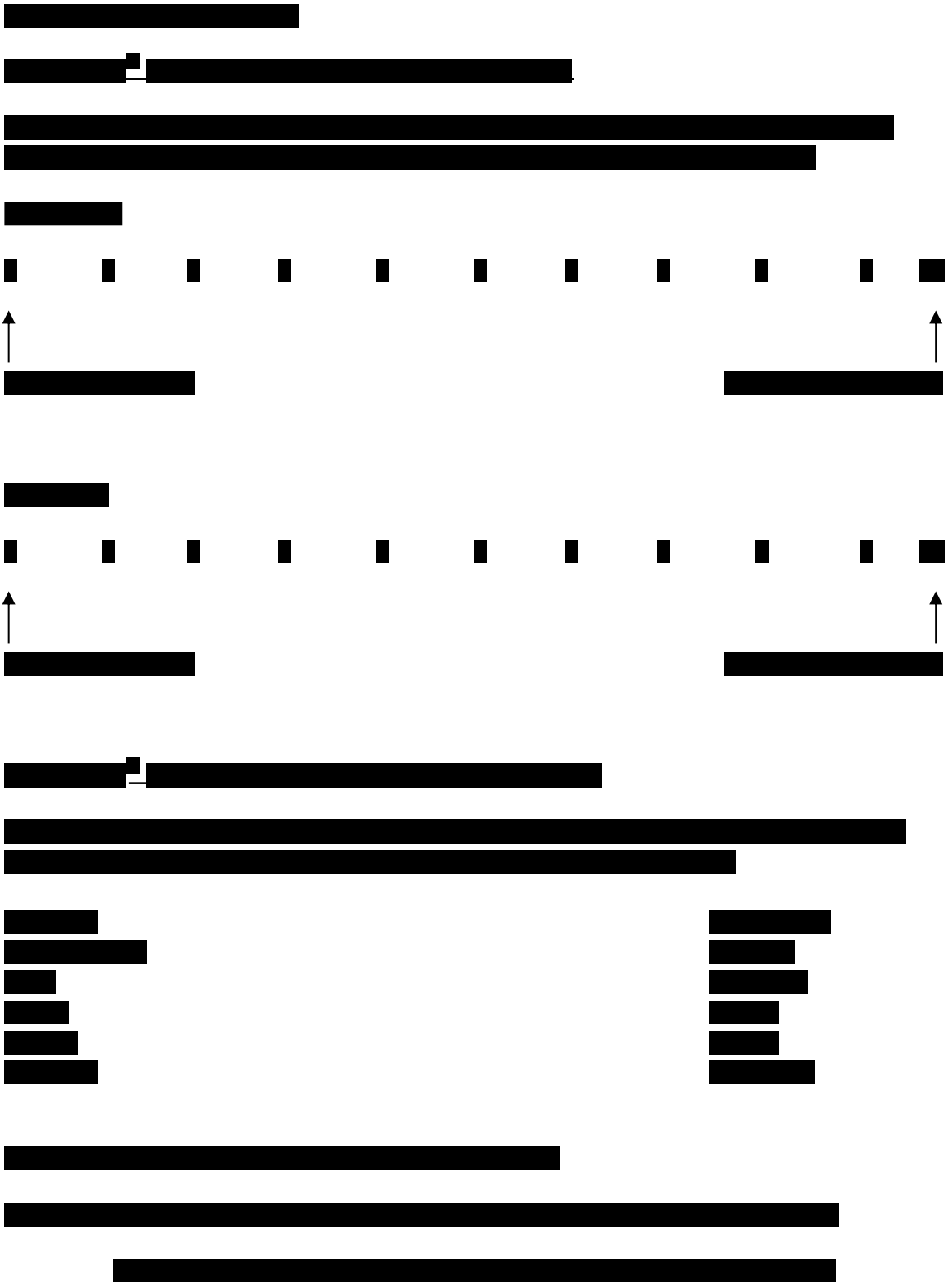

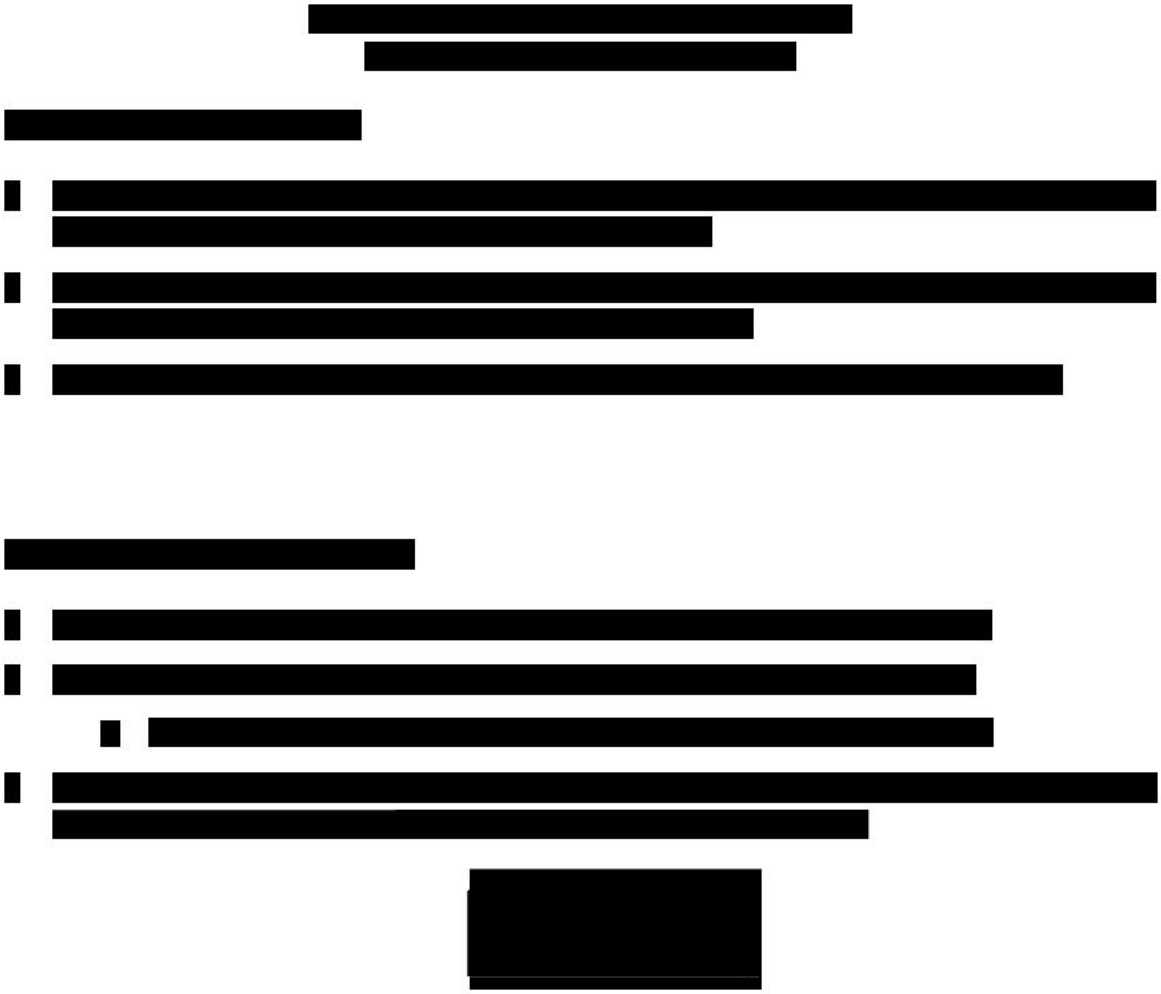

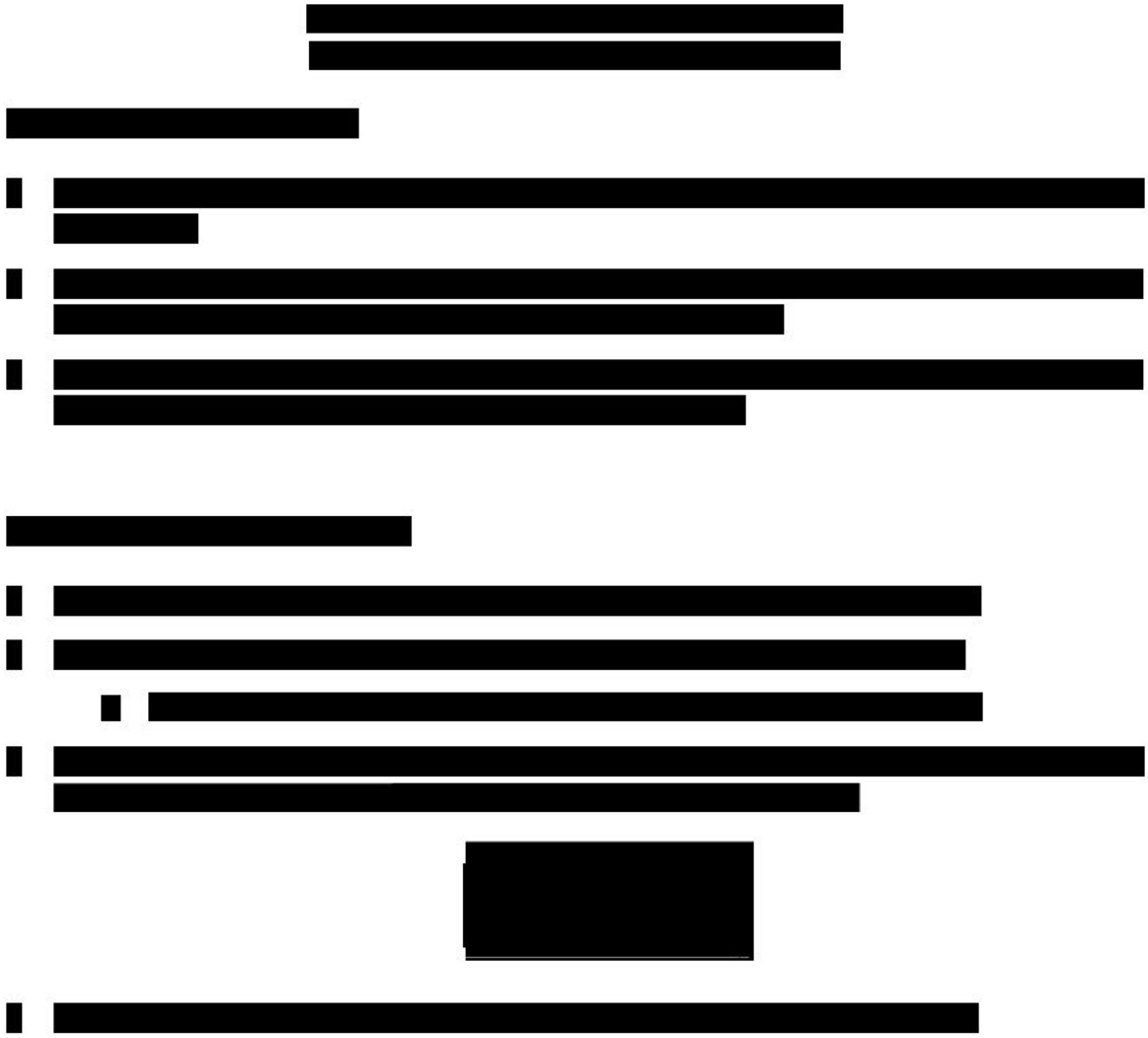

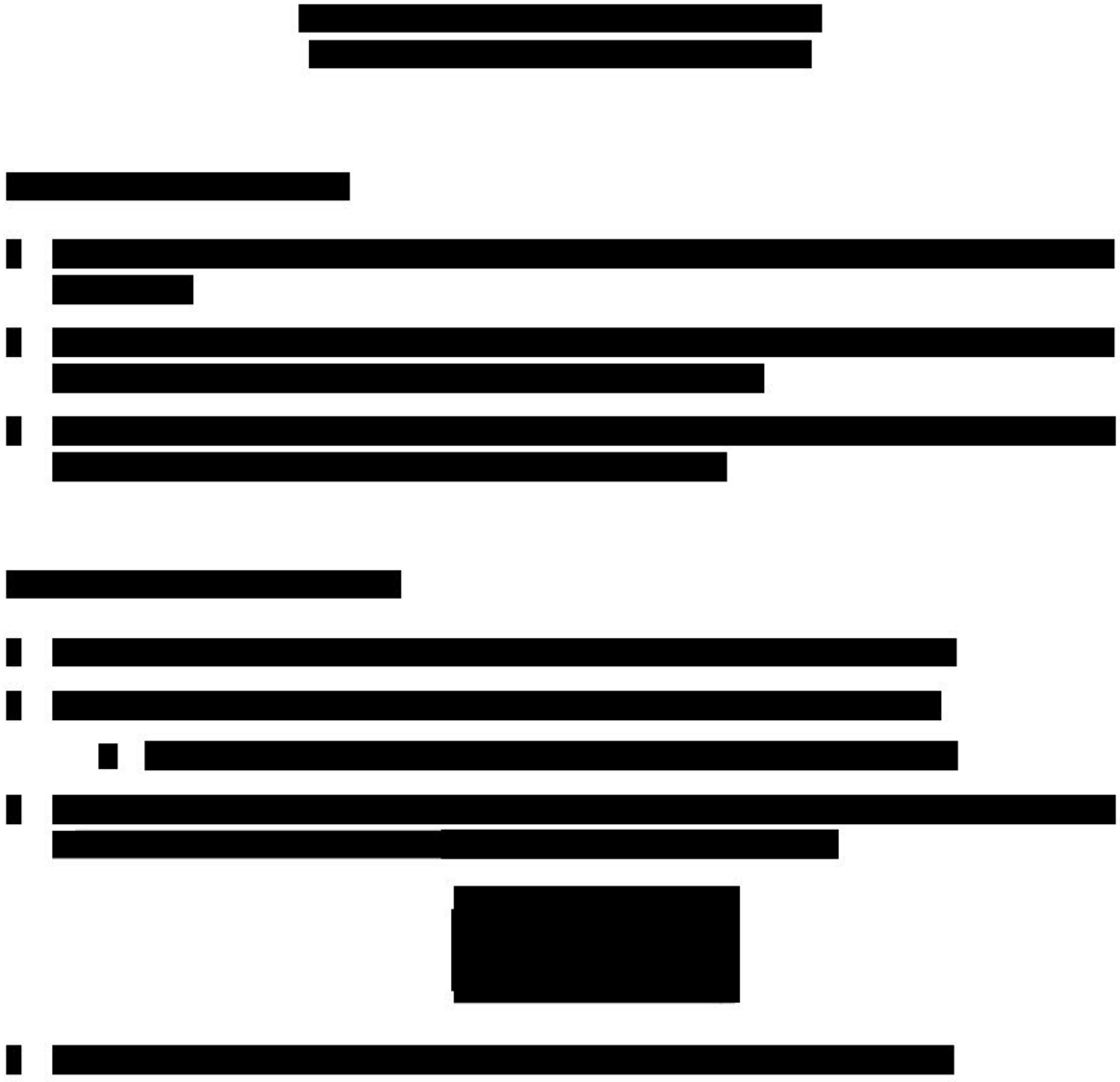

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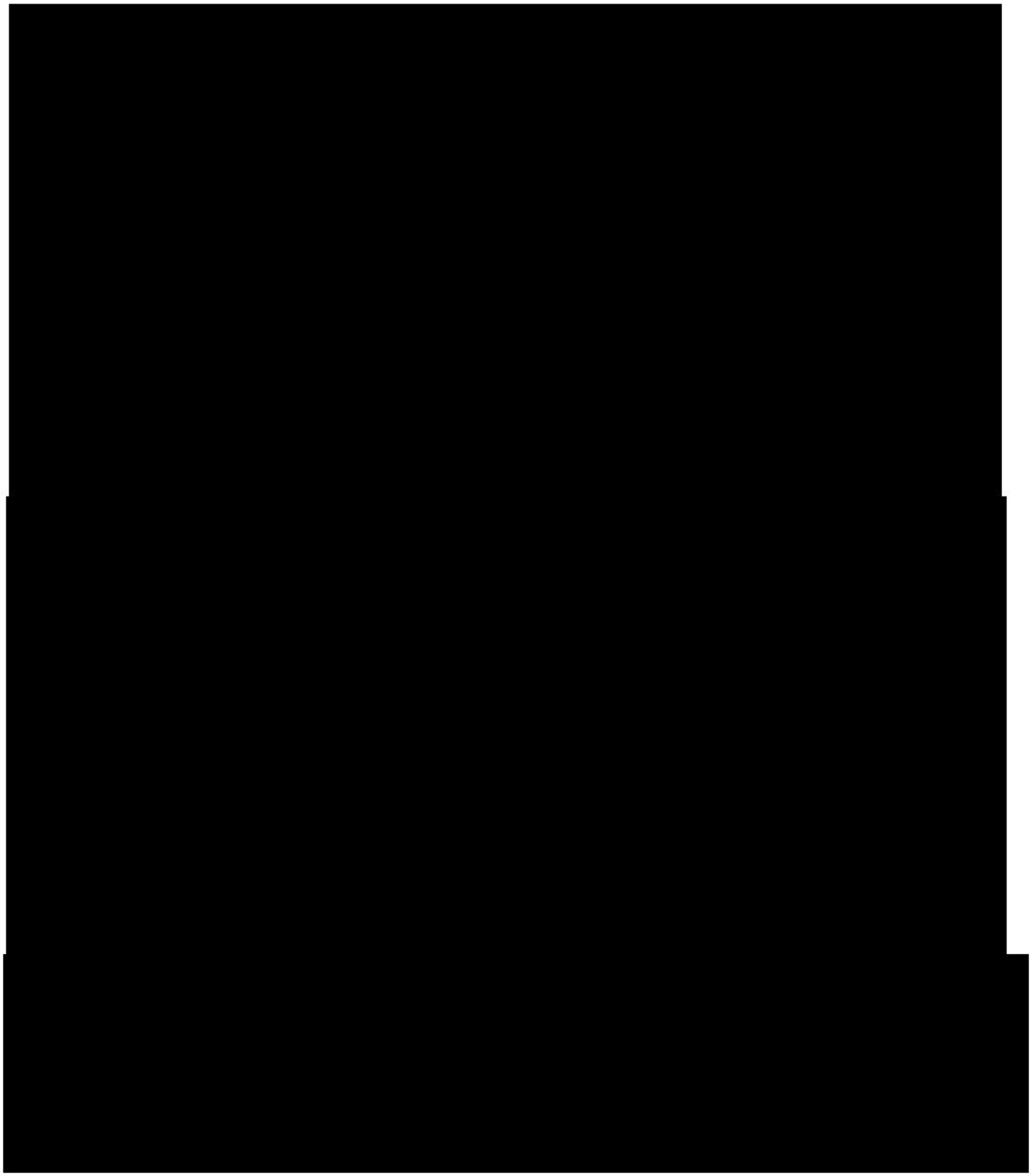
APPENDIX 4: HANDLING OF BIOLOGICAL SPECIMENS

Not Applicable.

APPENDIX 5: PROTOCOL AMENDMENT 2 SUMMARY



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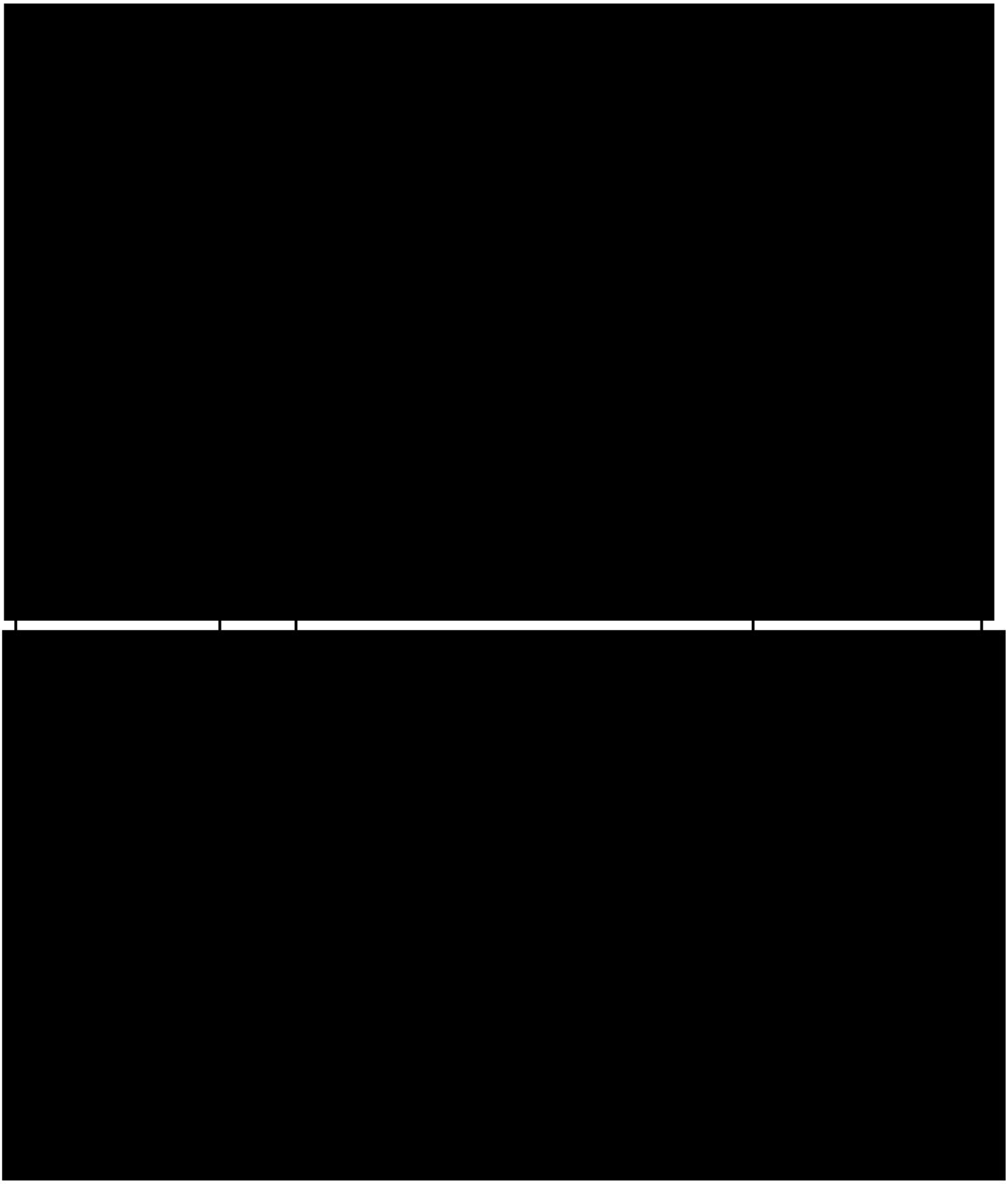

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