PROTOCOL ADX-102-AC-017

The INVIGORATE Trial: A SINGLE-CENTER, RANDOMIZED, DOUBLE-MASKED, CROSSOVER DESIGN, VEHICLE-CONTROLLED, PHASE 3 CLINICAL TRIAL TO ASSESS THE EFFICACY AND SAFETY OF REPROXALAP OPHTHALMIC SOLUTION (0.25%) COMPARED TO VEHICLE IN SUBJECTS WITH SEASONAL ALLERGIC CONJUNCTIVITIS USING THE ENVIRONMENTAL EXPOSURE CHAMBER (EEC)

PROTOCOL VERSION AND DATE: VERSION 6.0, 24 MAR 2021

ALDEYRA THERAPEUTICS, INC.
131 HARTWELL AVENUE, SUITE 320
LEXINGTON, MA 02421, U.S.A.

Sponsor Signature:

[redacted]

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

INVESTIGATOR STATEMENT

Protocol Number: ADX-102-AC-017

Protocol Title: The INVIGORATE Trial: A single-center, randomized, double-masked, crossover design, vehicle-controlled, Phase 3 clinical trial to assess the efficacy and safety of reproxalap ophthalmic solution (0.25%) compared to vehicle in subjects with seasonal allergic conjunctivitis using the environmental exposure chamber (EEC).

I understand that all information concerning reproxalap in connection with this clinical trial and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Trial Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) and I understand that any changes in the protocol must be approved in writing by Aldeyra Therapeutics, Inc., and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

I will use only the informed consent form approved by Aldeyra Therapeutics, Inc. and by my IRB/REB/IEC and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/IEC responsible for this study.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number ADX-102-AC-017, and will conduct the trial in accordance with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and applicable regulatory requirements.

PROTOCOL REVISION HISTORY

[redacted]

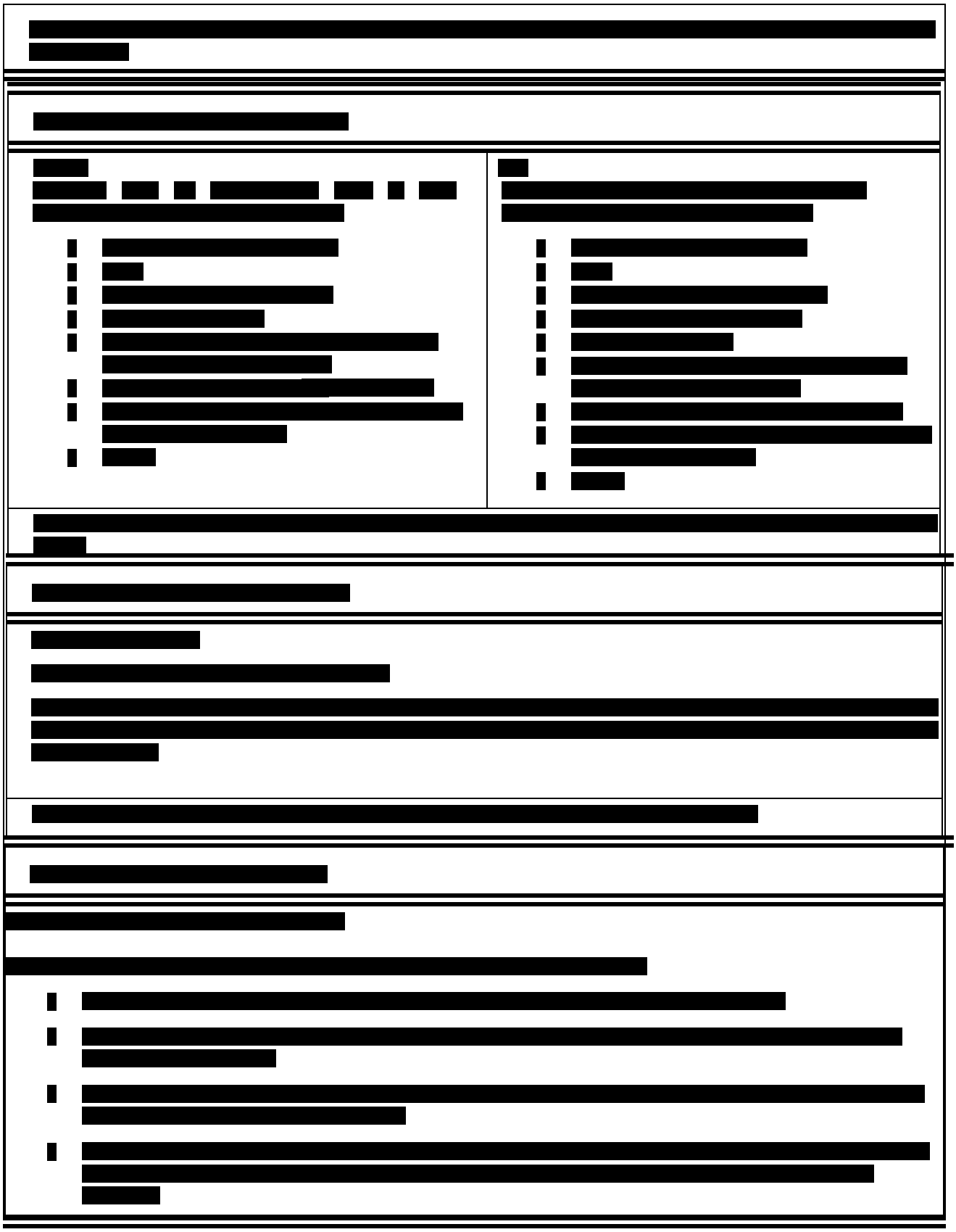
[redacted]

[redacted]

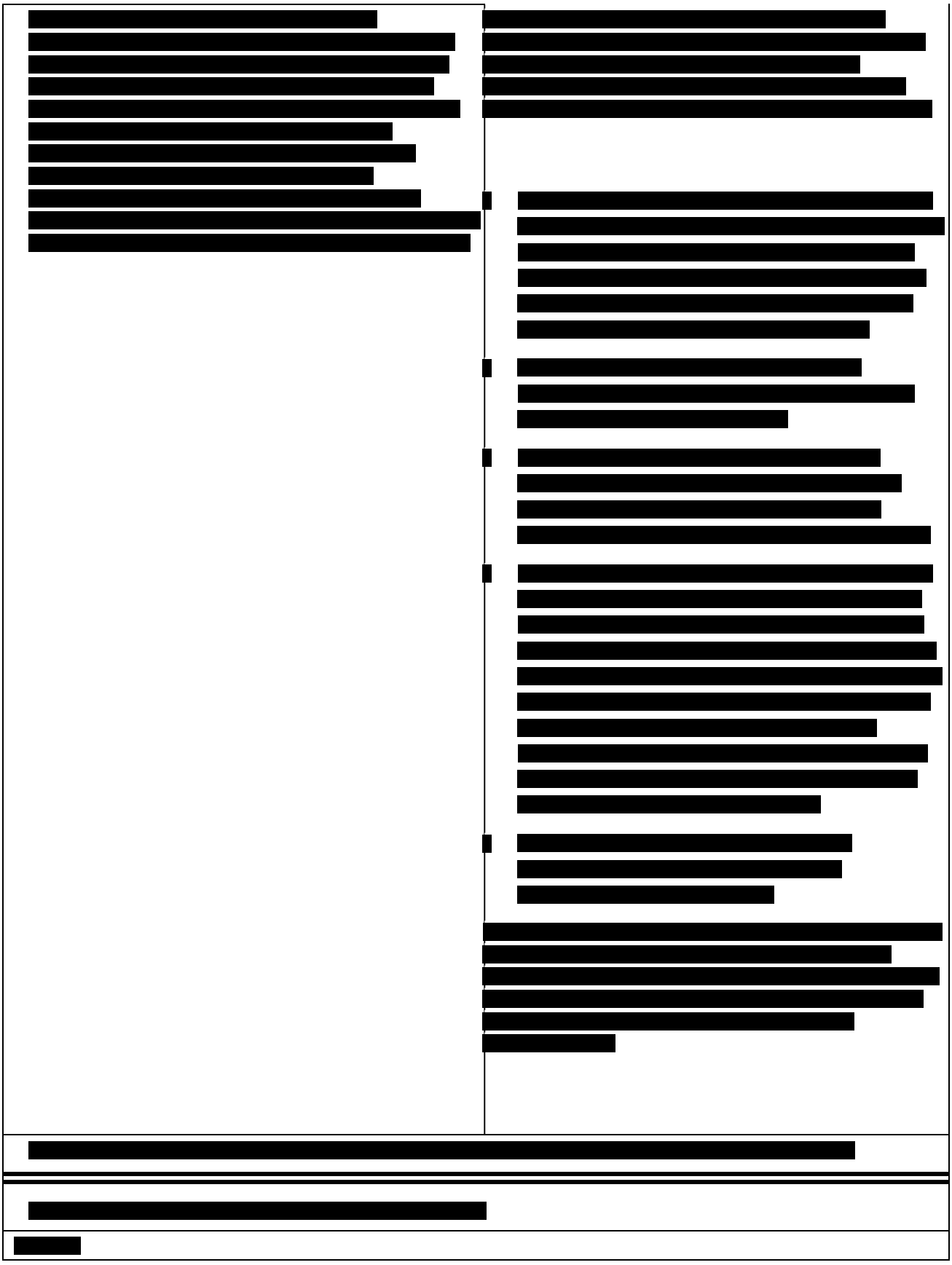
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

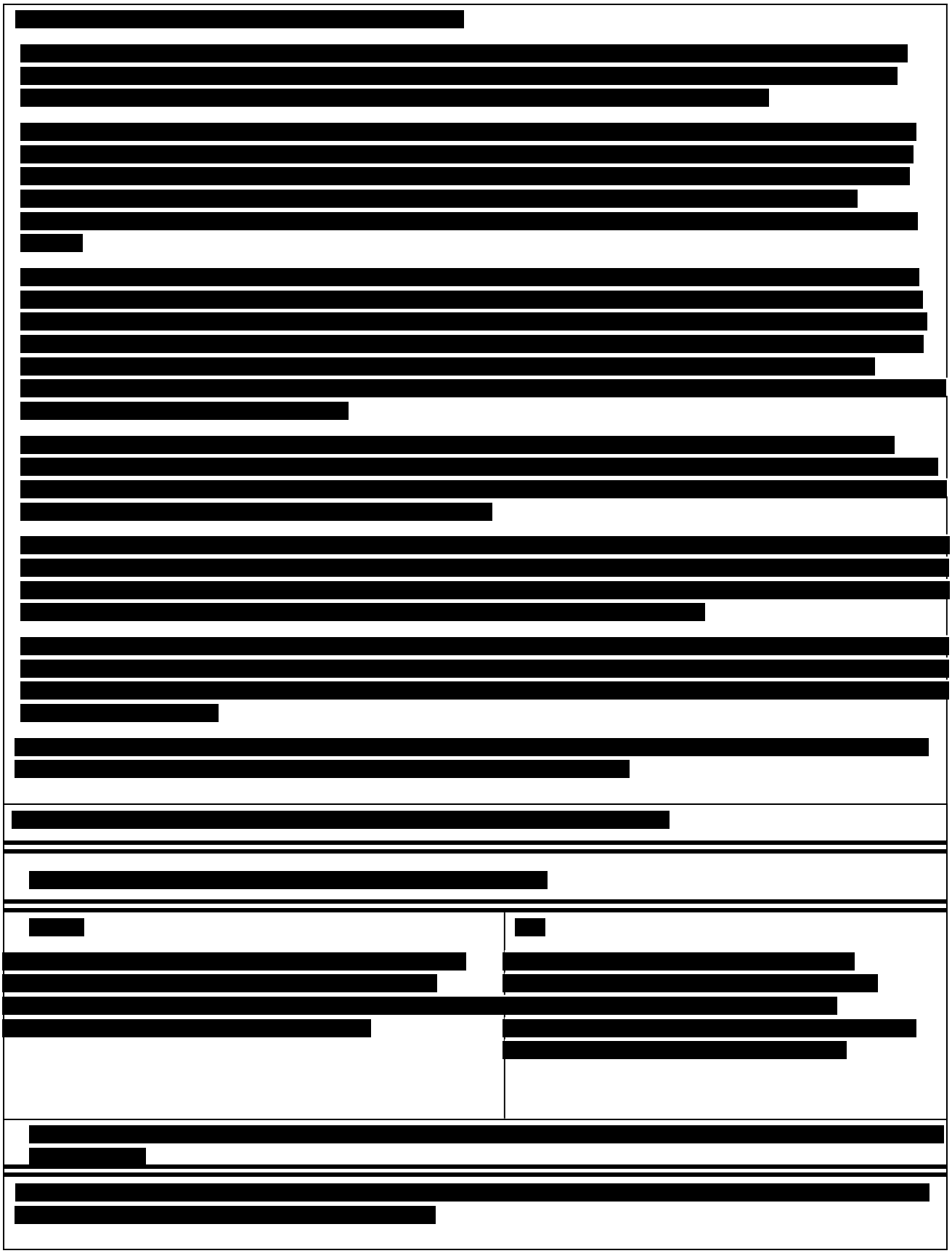
[redacted]

[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
Table 1 Schedule of Events and Assessments
[redacted]

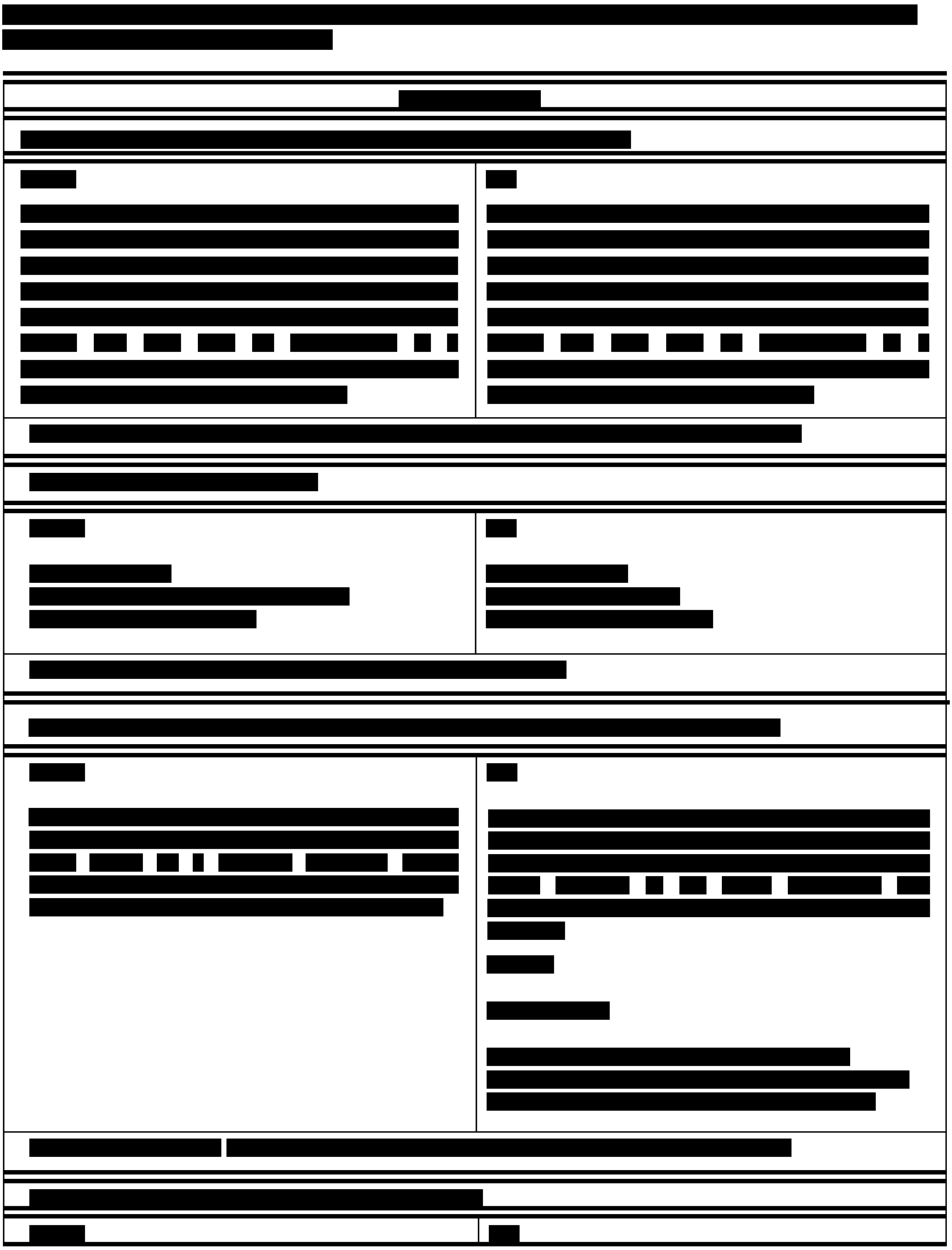


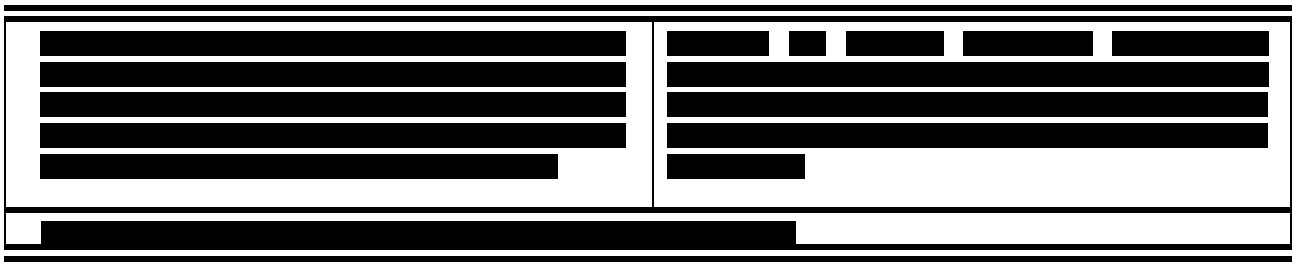
[redacted]





[redacted]





SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor Company:
Aldeyra Therapeutics, Inc.</td><td>Drug Under Study:
Reproxalap</td></tr>
<tr><td colspan="3">Title of Protocol: The INVIGORATE Trial: A single-center, randomized, double-masked, crossover design, vehicle-controlled, Phase 3 clinical trial to assess the efficacy and safety of reproxalap ophthalmic solution (0.25%) compared to vehicle in subjects with seasonal allergic conjunctivitis using the environmental exposure chamber (EEC).</td></tr>
<tr><td>Protocol Number:
Sponsor Study Code: ADX-102-AC-017
[redacted]Study Code: 19-MO-003-B</td><td>Phase:
3</td><td>Indication:
Allergic Conjunctivitis</td></tr>
<tr><td colspan="3">Subject Population: Subjects 18 years of age and older with allergic conjunctivitis</td></tr>
<tr><td colspan="3">Number of Subjects:
Approximately 670 subjects with seasonal allergic conjunctivitis to ragweed will be screened in order to randomize approximately 126 subjects, with approximately 100 subjects completing the trial.</td></tr>
<tr><td colspan="3">Number of Center(s):
One</td></tr>
<tr><td colspan="3">Test Products / Doses / Mode of Administration:
Eligible subjects will be randomized 1:1 to one of two treatment sequences of AB or BA where:
• Treatment A: Reproxalap Ophthalmic Solution (0.25%)
• Treatment B: Vehicle Ophthalmic Solution [redacted]
Approximately 126 subjects (approximately 63 per treatment sequence) will be enrolled.</td></tr>
<tr><td colspan="3">Criteria for Evaluation:
<u>Primary Endpoint:</u>
• Change from baseline in Ocular Itching score on a 9-point scale (0-4) from 110-210 minutes
<u>Key Secondary Endpoint:</u>
• Change from baseline in Conjunctival Redness on a 9-point scale (0-4) over the duration of the chamber (approximately 12 to 212 minutes)
<u>Secondary Endpoints:</u>
• Change from baseline in Tearing on a 4-point scale (0-3) over the duration of the chamber (approximately 10 to 210 minutes)
• Change from baseline in total ocular symptom score (TOSS, sum of itching, redness, and tearing scores) on an 11-point composite score over the duration of the chamber (approximately 10 to 212 minutes)
<u>Safety Measures:</u>
• Adverse Events (reported, elicited, and observed)
• Snellen Visual Acuity (VA)
• Slit Lamp Examination (SLE)
• Non-contact Intraocular Pressure Tonometry (NCT), as detailed in Table 1.</td></tr>
</table>

- Dilated and undilated fundus examination

Study Design:

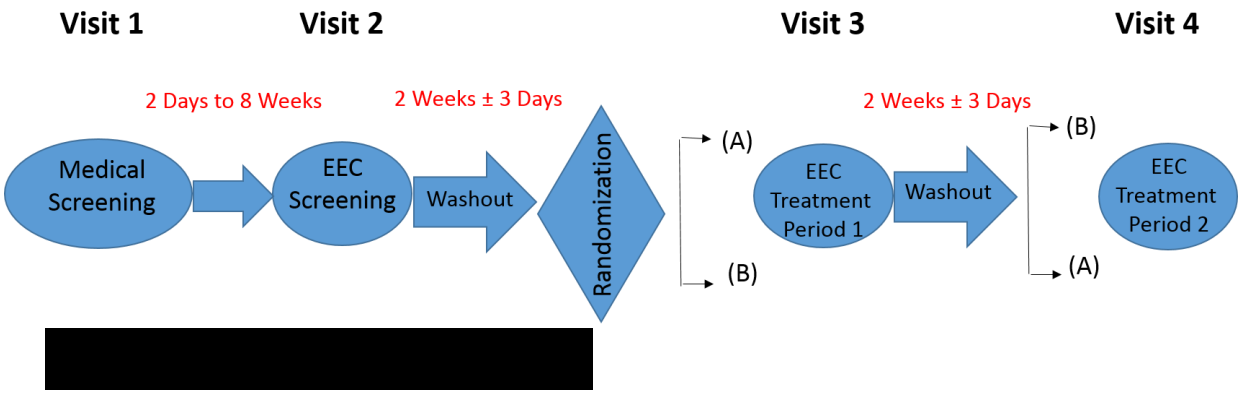
The double-masked, vehicle-controlled, randomized, two-way crossover clinical trial allows for the testing of Reproxalap Ophthalmic Solution (0.25%) versus Vehicle Ophthalmic Solution in subjects with ragweed-induced allergic conjunctivitis in the EEC.

The clinical trial consists of four visits to the clinic (one Medical Screening visit, one Screening EEC visit, and two EEC treatment visits). The EEC sessions will be separated by an approximate two-week washout period to ensure adequate elimination of responses caused by allergen exposure in the EEC and allow the recuperation of mast cells.

The EEC clinical research facility is a room designed with the capacity and control mechanisms to expose participants to airborne ragweed pollen grains and maintains target temperature and relative humidity throughout.

The EEC has 100% fresh HEPA-filtered clean air to which commercially obtained air dried, non-defatted short ragweed (Ambrosia *artemesiifolia*) pollen (Greer Laboratories, Lenoir, NC) will be introduced and circulated throughout the room with tight humidity and temperature controls as described previously (Ronborg et al 1996). While subjects are in the EEC, the average sessional airborne ragweed pollen counts will be maintained at 3500 ± 500 grains per cubic meter by continuous monitoring and feedback regulation of the pollen emission measured. The controlled pollen challenge, over time, allows evaluation of subject responses at any time-point throughout the challenge process.

Study Design



(A): Reproxalap 0.25% ophthalmic solution
(B): Vehicle Ophthalmic Solution

At the **Medical Screening Visit (Visit 1)** occurring between 2 days to 8 weeks prior to Visit 2, subjects will undergo the informed consent process, and information about demographics, baseline characteristics, medical history, social history, physical examination will be performed, and concomitant medication will be collected. Vital signs and samples for standard clinical safety laboratory tests will be obtained. A urine pregnancy test will be administered to women of childbearing potential (WOCBP). Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination) to ensure initial eligibility criteria are met. A skin prick test for a panel of test allergens will be conducted; results must be positive (i.e., a wheal that is 3 mm greater than the negative control) for at least one test allergen and must include ragweed in order to proceed to Visit 2.

At the **EEC Screening Visit (Visit 2),** qualified site staff will update concomitant medications, collect AEs, as applicable and collect vital signs. A urine pregnancy test will be administered to WOCBP. Fundus exam

(un-dilated), Snellen VA, SLE, subject rating of symptoms, and staff grading of conjunctival redness will be performed to ensure the anterior segment of the eye is healthy. [redacted]

At all EEC sessions, assessments of ophthalmic evaluations will be collected [redacted]. In the event of an [redacted] failure, paper diary cards will be used as a back-up to collect symptom scores. Itching will be rated by the subject on the [redacted] using a 9-point, discrete, scale (i.e, 0-4 with 0.5 increments). For subject rated ocular tearing, a 4-point scale (0-3) will be employed. For staff-assessed grading of conjunctival redness, a standard 9-point scale (i.e., 0-4 with 0.5 unit increments) will be employed. Additionally, Total Ocular Symptom Score (TOSS) is a composite score of ocular itching (0 – 4), ocular tearing (0 – 3) and ocular redness (0 – 4) with a maximum score of 11 units will be analyzed.

[redacted]

Visit 2 Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing [redacted], and

2) Staff-assessed conjunctival redness will be recorded [redacted].

Visit 2 Post-EEC entry:

1) Subject assessment for ocular itching and tearing [redacted].

2) Staff-assessed conjunctival redness will be recorded at [redacted].

[redacted]

At the **Randomization/Treatment EEC Session One (Visit 3),** qualified site staff will update concomitant medications, collect AEs as applicable, and collect vital signs. A urine pregnancy test will be administered to WOCBP. Ophthalmic evaluations will be conducted (Fundus exam, Snellen VA, NCT, SLE, subject rating of symptoms, and staff grading of conjunctival redness). [redacted]

Subjects will be randomized to receive a first dose of either Reproxalap Ophthalmic Solution (0.25%) (Treatment A) or Vehicle Ophthalmic Solution (Treatment B). Qualified site staff will instill one drop of the randomized treatment into each eye at approximately time zero [redacted] prior to entry to the EEC after all the pre-EEC assessments are done.

Visit 3 Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing will be recorded [redacted] and

2) Staff-assessed conjunctival redness will be recorded [redacted].

Visit 3 Post-EEC entry:

1) Subject assessment for ocular itching and tearing will occur [redacted].

2) Staff-assessed conjunctival redness will be recorded [redacted].

At approximately 90-minutes post-EEC entry (and after subject assessed itching and tearing and staff assessed conjunctival redness for all time-points post first dose have been completed), a second dose (one drop in each eye) of the same randomized treatment will be administered in each eye by the qualified site staff. Subject will continue to assess symptoms of ocular itching and tearing after the second dose [redacted], and staff-assessed conjunctival redness will be recorded [redacted].

Visit 3 Post-EEC exit (at approximately t = 215 minutes):

1) Subject assessment for ocular itching and tearing will occur [redacted].

2) Staff-assessed conjunctival redness will be recorded [redacted].

At the **Treatment EEC Session Two (Visit 4),** all procedures performed at Visit 3 will be repeated except that each subject will be given a different treatment depending on the treatment sequence the subject was randomized to [Reproxalap Ophthalmic Solution (0.25%) (Treatment A) or Vehicle Ophthalmic Solution (Treatment B)]. Before EEC entry, a urine pregnancy test will be administered to WOCBP.

Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination), clinical safety labs and vital signs will be collected to ensure safety prior to exit of the clinical trial.

Criteria for Inclusion:

Each subject must:

- Be at least 18 years of age at the time of screening of either sex or any race;
- Provide written informed consent;
- Be willing and able to follow instructions, and can attend all required clinical trial visits;
- Have at least a two-year history of moderate-to-severe ragweed-induced allergic conjunctivitis based on investigator's judgement;
- Have a positive skin prick test to ragweed pollen within the past year of the Medical Screening Visit (Visit 1);
- [redacted]
- [redacted]
- [redacted]

- Confirmed absence of pregnancy according to a negative urine pregnancy test at the Medical Screening Visit (Visit 1);
- WOCBP must agree to use a reliable and highly effective method of birth control with a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or vasectomized partners) during the clinical trial, as judged by the investigator.

Criteria for Exclusion:

Each subject must not:

- [redacted]
- [redacted]
- Have worn contact lens within two weeks prior to the Baseline EEC Screening Visit (Visit 2) and are unwilling to discontinue use for the duration of the study
- Have a history of blepharitis, dry eye syndrome, herpes simplex keratitis, or herpes zoster keratitis;
- Have a history of uveitis in the past three years;
- Have a presence of any ocular infection (bacterial, viral, or fungal) or active ocular inflammation (e.g., follicular conjunctivitis, allergic conjunctivitis) within 14 days prior to the Medical Screening Visit (Visit 1);
- Have a presence of any chronic ocular degenerative condition or ocular inflammation that, in the opinion of the investigator, is likely to worsen over the course of the clinical trial;
- [redacted]

[redacted]

- Use any prescription or over-the-counter topical ocular medications during the clinical trial;
- Use of any medication not previously specified that impairs either allergy skin testing or EEC evaluation at the discretion of the Investigator;
- Have history of moderate-to-severe asthma (a score of greater than Global Initiative of Asthma (GINA) Score of 1) or allergy-induced asthma to ragweed;
- Have systemic signs of infection (e.g., fever, current treatment with antibiotics);
- Have a systemic disease or uncontrolled medical condition, which, in the opinion of the investigator, could interfere with clinical trial measurements or subject compliance. Such diseases or conditions would include, but are not limited to, cancer, alcoholism, drug dependency or abuse, or psychiatric disease;

[redacted]

- WOCBP who are pregnant, nursing, or not using an effective means of contraception;

[redacted]

- Have received an investigational product in the last 30 days prior to the baseline EEC visit (Visit 2);
- Have a clinically relevant sensitization to other allergens if clinical symptoms are expected to interfere during the study, at the discretion of the investigator;

[redacted]

[redacted]

Statistical Analysis:

Approximately 670 subjects with ragweed-induced, moderate-to-severe allergic conjunctivitis will be screened in order to randomize approximately 126 subjects, and for approximately 100 subjects to complete the study. Approximately sixty-three (63) subjects will be assigned to each of two (2) treatment sequences, AB and BA.

[redacted]

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses and will dominate any statistical analysis described herein. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc.

The efficacy analyses of all efficacy endpoints will be carried out in the Intent-to-Treat (ITT) population. Supportive analyses may also be provided for Itching endpoint(s) using the Per-Protocol (PP) population.

For the primary efficacy endpoint, Reproxalap Ophthalmic Solution (0.25%) will be compared to vehicle. Treatment comparisons at pre-specified time points (every 10 minutes from 110 to 210 minutes following chamber entry) will be performed by using a Mixed Model Repeated Measures (MMRM) approach for a crossover study with 2 periods.

Secondary efficacy endpoints will be analyzed by using a similar approach as the primary efficacy variable, except over the duration of the chamber (approximately 10 to 212 minutes), as assessed by a single p value for the treatment term. Further details of the analysis plan will be described in statistical analysis plan document (SAP).

Table 1. Schedule of Events and Assessments

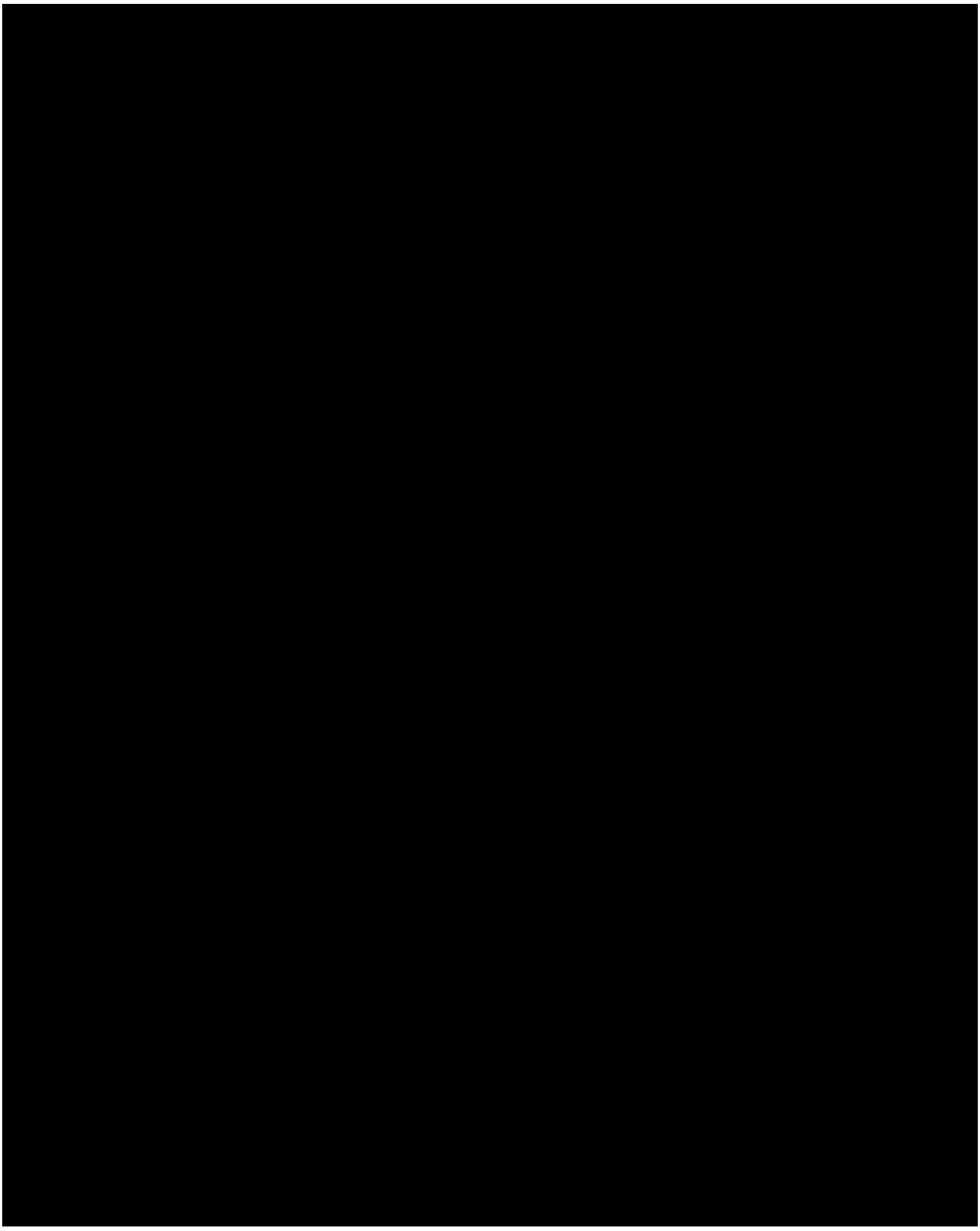


Table 2. Schedule of Subject Assessed Itching and Tearing

[redacted]

Table 3. Schedule of Staff-Assessed Conjunctival Redness Recording

[redacted]

Table 4. Schedule of Subject Assessed Itching and Tearing Post-EEC Exit (starting at approximately t = 215)

Table 5. Schedule of Staff-Assessed Conjunctival Redness Recording Post-EEC Exit (starting at approximately t = 215)

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Allergic conjunctivitis
AE	Adverse event
ANCOVA	Analysis of Covariance
AUC	Area under the curve
BP	Blood Pressure
CFB	Change from baseline
COVID-19	Corona Virus Disease 2019
CRF	Case report form
CTA	Clinical Trial Application
EEC	Environmental Exposure Chamber
EDC	Electronic data capture
[redacted]	[redacted]
GCP	Good Clinical Practice
GINA	Global Initiative of Asthma
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational product
IUD	Intrauterine device
MMRM	Mixed Model Repeated Measures
NCT	Non-contact IOP tonometry
QID	Four times daily
[redacted]	[redacted]
PCR	Polymerise Chain Reaction
RASP	Reactive Aldehyde Species
RR	Respiratory Rate
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
[redacted]	[redacted]
SD	Standard deviation
SLE	Slit lamp examination
TOSS	Total ocular symptom score
VA	Visual acuity
VAS	Visual analog scale
[redacted]	[redacted]
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Allergic Conjunctivitis

[redacted]

1.2 Therapeutic Rationale for Reproxalap in Allergic Conjunctivitis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3 Clinical Trials of Reproxalap

[redacted]

[redacted]

[redacted]

1.4 Rationale for Use of the Allergy Environmental Exposure Chamber (EEC)

[redacted]

1.5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.6 [redacted]

[redacted]

[redacted]

1.7 [redacted]

[redacted]

2 CLINICAL TRIAL OBJECTIVE AND ENDPOINTS

2.1 Primary Objective

The primary objective of the clinical trial is:

- To evaluate the efficacy and safety of Reproxalap Ophthalmic Solution (0.25%) compared to Vehicle Ophthalmic Solution for the treatment of allergic conjunctivitis using the EEC clinical trial design

2.2 Clinical Trial Assessments and Endpoints

The double-masked, vehicle-controlled, randomized, two-way crossover, Phase 3 clinical trial will evaluate the efficacy of Reproxalap Ophthalmic Solution (0.25%) versus Vehicle Ophthalmic Solution in subjects with ragweed-induced allergic conjunctivitis in the EEC.

Ocular itching will be rated by the subject [redacted] using a 9-point, discrete, 0-4 scale with 0.5 increments as shown below.

[redacted]

*0.5 increments between each score are permitted in this scale.

Tearing will be rated by the subject [redacted] using a 4-point discrete 0-3 scale as shown below.

[redacted]

Figure 5. Photographic Ocular Redness

[redacted]

[redacted]

*0.5 increments between each score are permitted in this scale.

Total Ocular Symptom Score (TOSS) is a composite score of ocular itching (0 – 4), ocular tearing (0 – 3) and ocular redness (0 – 4) with a maximum score of 11 units.

2.3 Efficacy Endpoints:

The change from baseline will be derived for each treatment visit between approximately 10-212 minutes and will be used to assess the activity of Reproxalap Ophthalmic Solution.

Primary Endpoint:

- Change from baseline in Ocular Itching score on a 9-point scale (0-4) from 110-210 minutes

Key Secondary Endpoint:

- Change from baseline in Conjunctival Redness on a 9-point scale (0-4) over the duration of the chamber (approximately 12 to 212 minutes)

Secondary Endpoints:

- Change from baseline in Tearing on a 4-point scale (0-3) over the duration of the chamber (approximately 10 to 210 minutes)
- Change from baseline in TOSS on an 11-point composite score (sum of itching, tearing, and redness) over the duration of the chamber (approximately 10 to 212 minutes)

2.4 Safety Endpoints

Safety assessments will include Snellen visual acuity (VA), slit lamp examination (SLE) and non-contact intraocular pressure tonometry (NCT) as detailed in Table 1. Dilated fundus examination at screening Visit 1 and at Visit 4 and undilated fundus examination will be performed at Visits 2 and 3. Adverse event (AEs; reported, elicited and observed) assessments will be performed at Visit 2 through Visit 4.

3 INVESTIGATIONAL PLAN

3.1 Overall Clinical Trial Design and Plan

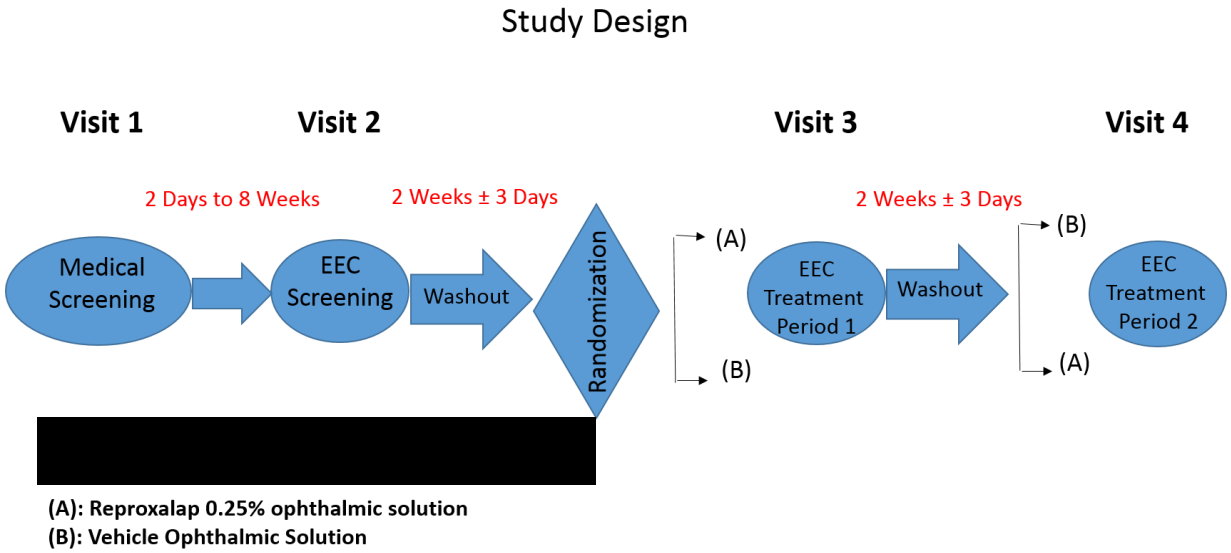
The double-masked, vehicle-controlled, randomized, two-way crossover clinical trial allows for the testing of Reproxalap Ophthalmic Solution (0.25%) versus Vehicle Ophthalmic Solution in subjects with ragweed-induced allergic conjunctivitis in the EEC.

The clinical trial consists of four visits to the clinic (one Medical Screening visit, one Screening EEC visit, and two EEC treatment visits).The three EEC sessions (one EEC screening and two EEC treatment sessions) will be separated by an approximate two-week washout period to ensure adequate elimination of responses caused by allergen exposure in the EEC and allow the recuperation of mast cells, please refer to Figure 6.

The EEC clinical research facility is a room designed with the capacity and control mechanisms to expose participants to airborne ragweed pollen grains and maintains target temperature and relative humidity throughout.

The use of the controlled EEC allergen exposure has been validated to provide spatial and temporal airborne allergen uniformity and to mimic the natural exposure on a peak allergen day.

Figure 6. Clinical Trial Design



At the **Medical Screening Visit (Visit 1),** subjects will undergo the informed consent process, and information about demographics, baseline characteristics, medical history, social history, physical examination will be performed and concomitant medication will be collected. Vital signs and samples for standard clinical safety laboratory tests will be obtained. A urine pregnancy test will be administered to women of childbearing potential (WOCBP).

Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination) to ensure initial eligibility criteria are met. A skin prick test for a panel of test allergens will be conducted; results must be positive (i.e., a wheal that is 3 mm greater than the negative control) for at least one test allergen and must include ragweed in order to proceed to Visit 2.

At all EEC sessions, assessments of ophthalmic evaluations will be collected [redacted] Wilson et al., 2014). In the event of an [redacted] failure, paper diary cards will be used as a back-up to collect symptom scores. For subject-reported symptoms of ocular itching, a standard 9 point (i.e., 0-4 with 0.5 unit increments) scale will be employed. For staff-assessed grading of conjunctival redness, a standard 9-point (i.e., 0-4 with 0.5 unit increments) will be employed. [redacted]

At the **EEC Screening Visit (Visit 2),** qualified site staff will update concomitant medications and collect AEs, as applicable and perform tests for vital signs. A urine pregnancy test will be administered to WOCBP. Fundus exam, Snellen VA, SLE, subject rating of symptoms, and staff

grading of conjunctival redness will be performed to ensure the anterior segment of the eye is healthy. [redacted]

Visit 2 Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing will be recorded [redacted], and

2) Staff-assessed conjunctival redness will be recorded [redacted].

Visit 2 Post-EEC entry:

1) Subject assessment for ocular itching and tearing will occur [redacted].

2) Staff-assessed conjunctival redness will be recorded [redacted].

Please refer to Table 2, Table 3, Table 4, and Table 5 for schedule of staff and subject assessment time-points.

[redacted]

At the **Randomization/Treatment EEC Session One (Visit 3),** qualified site staff will update concomitant medications, collect AEs, as applicable and collect vital signs. A urine pregnancy test will be administered to WOCBP. Ophthalmic evaluations will be conducted (Fundus exam, Snellen VA, NCT SLE, subject rating of symptoms, and staff grading of conjunctival redness). [redacted]

Subjects will be randomized to receive a first dose of either Reproxalap Ophthalmic Solution (0.25%) (Treatment A) or Vehicle Ophthalmic Solution (Treatment B). Qualified site staff will instill one drop of the randomized treatment into each eye at approximately time zero [redacted] prior to entry to the EEC after all the pre-EEC assessments are done.

Visit 3 Pre-EEC entry (Baseline):

1) Subject assessment for ocular itching and tearing will be recorded [redacted], and

2) Staff-assessed conjunctival redness will be recorded [redacted].

Visit 3 Post-EEC entry:

1) Subject assessment for ocular itching and tearing will occur [redacted].

2) Staff-assessed conjunctival redness will be recorded [redacted].

At approximately 90-minutes post-EEC entry (and after subject assessed itching and tearing and staff assessed conjunctival redness for all time-points post first dose have been completed), a second dose (one drop in each eye) of the same randomized treatment will be administered in each eye by the qualified site staff. Subject will continue to assess symptoms of ocular itching and tearing after the second dose [redacted] and staff-assessed conjunctival redness will be recorded at approximately post second dose [redacted].

Visit 3 Post-EEC exit (starting at approximately t = 215 minutes):

1) Subject assessed ocular itching and tearing will continue [redacted];

2) Staff assessed conjunctival redness will continue to be recorded post-EEC exit [redacted].

Subjects will be asked to return in at least two weeks for Visit 4.

At the **Treatment EEC Session Two (Visit 4),** all procedures performed at Visit 3 will be repeated except that each subject will be given a different treatment dependent on the treatment sequence the subject was randomized to [Reproxalap Ophthalmic Solution (0.25%) (Treatment A) or Vehicle Ophthalmic Solution (Treatment B)].

Before EEC entry, a urine pregnancy test will be administered to WOCBP.

Subjects will undergo ophthalmic examinations (Snellen VA, SLE, NCT, and a dilated fundus examination), clinical safety lab tests and vital signs will be collected to ensure safety prior to exit of the clinical trial.

3.2 Assigning Subjects to Treatment Groups

3.2.1 Subject Numbering

Each subject screened for the clinical trial will be assigned a unique subject number that will be used to identify the subject throughout subject participation in the clinical trial. If a subject fails to be randomized, the reason should be documented in the source documents and case report form (CRF). The subject will be considered a screen failure.

3.2.2 Randomization

Eligible subjects will be randomized 1:1 to one of two treatment sequences of AB or BA, where:

- Treatment A: Reproxalap Ophthalmic Solution (0.25%)
- Treatment B: Vehicle Ophthalmic Solution

Approximately 126 subjects (approximately 63 per treatment sequence) will be enrolled.

3.3 Masking and Unmasking

3.3.1 Masking

Investigators, qualified site personnel, and subjects will be masked to the investigational product (IP) administered. The Sponsor will also be masked to the IP administered until database lock.

3.3.2 Emergency Unmasking

Emergency unmasking should only be performed when necessary to treat the subject. Most often, knowledge of the possible treatment assignments is sufficient to treat a clinical trial subject who presents with an emergency condition.

The investigator should make every effort to contact the Medical Monitor to discuss the subject's emergency and the need to unmask, prior to unmasking any subject.

In situations in which the investigator has tried but is unable to reach the Medical Monitor, best judgement on the part of the investigator should be used, based on the nature and urgency of the clinical situation, and may proceed with unmasking without having successfully reached and discussed the situation with the Medical Monitor. Once a subject's treatment assignment has been unmasked, the Medical Monitor should be notified within 24 hours of unmasking of the treatment, without revealing the treatment.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's IP kit, which contains a scratch-off laminate under which the treatment is identified, along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject.

The emergency unmasking should be performed by the designated site personnel. 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 the protocol. The investigator has the responsibility to contact the Sponsor or designee within 24 hours of unmasking. In the event of a drug-related, serious, unexpected AE, the Sponsor's Pharmacovigilance Department or designee will be provided with the treatment assignment for the subject for regulatory reporting.

If treatment assignment is unmasked, the treatment will be discontinued immediately, and the subject will be discontinued from the clinical trial.

The mask may be broken in the case of a pregnancy should the subject desire this information.

3.4 Safety Oversight

During the clinical trial, subject safety will be monitored on a continuous basis by the Medical Monitor until the last subject completes the last scheduled clinical trial assessment.

3.5 Clinical Trial Duration for Individual Subjects

The clinical trial consists of four clinic visits over a period of approximately 12 weeks.

4 CLINICAL TRIAL POPULATION SELECTION

4.1 Inclusion Criteria

In order to be considered eligible for the clinical trial, subjects must:

1. Be at least 18 years of age at the time of screening of either sex or any race;
2. Provide written informed consent;
3. Be willing and able to follow instructions, and can attend all required clinical trial visits;
4. Have at least a two-year history of moderate-to-severe ragweed-induced allergic conjunctivitis based on Investigator's judgement;
5. Have a positive skin prick test to ragweed pollen within the past year of the Medical Screening Visit (Visit 1);

[redacted]

9. Confirmed absence of pregnancy according to a negative urine pregnancy test at the Medical Screening Visit (Visit 1);
10. WOCBP must agree to use a reliable and highly effective method of birth control with a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or vasectomized partners) during the clinical trial, as judged by the investigator.

4.2 Exclusion Criteria

Subjects must not:

[redacted]

[redacted]

3. Have worn contact lens within two weeks prior to the Baseline EEC Screening Visit (Visit 2) and are unwilling to discontinue use for the duration of the study;
4. Have a history of blepharitis, dry eye syndrome, herpes simplex keratitis, or herpes zoster keratitis;
5. Have a history of uveitis in the past three years;
6. Have a presence of any ocular infection (bacterial, viral, or fungal) or active ocular inflammation (e.g., follicular conjunctivitis, allergic conjunctivitis) within 14 days prior to the Medical Screening Visit (Visit 1);
7. Have a presence of any chronic ocular degenerative condition or ocular inflammation that, in the opinion of the investigator, is likely to worsen over the course of the clinical trial;

[redacted]

9. Use any prescription or over-the-counter topical ocular medications during the clinical trial;
10. Use of any medication not previously specified that impairs either allergy skin testing or EEC evaluation at the discretion of the investigator;
11. Have history of moderate-to-severe asthma (a score of greater than Global Initiative of Asthma (GINA) Score of 1) or allergy-induced asthma to ragweed;
12. Have systemic signs of infection (e.g., fever, current treatment with antibiotics);
13. Have a systemic disease or uncontrolled medical condition, which, in the opinion of the investigator, could interfere with clinical trial measurements or subject compliance. Such

diseases or conditions would include, but are not limited to, cancer, alcoholism, drug dependency or abuse, or psychiatric disease;

[redacted]

15. WOCBP who are pregnant, nursing, or not using an effective means of contraception;

[redacted]

20. Have received an investigational product in the last 30 days prior to the baseline EEC visit (Visit 2);
21. Have a clinically relevant sensitization to other allergens if clinical symptoms are expected to interfere during the study, at the discretion of investigator;

[redacted]

5 SUBJECT DISPOSITION

5.1 Completed Subjects

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

5.2 Discontinued Subjects

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

- Subject request/withdrawal;
- AEs;
- Positive COVID-19 test result;
- Positive pregnancy results;
- Protocol violations;
- Administrative reasons (e.g., inability to continue, lost to follow-up);
- Sponsor termination of the clinical trial;
- Any sound medical reason, as determined by the investigator; or
- Other.

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor or designee and will be clearly documented on the eCRF. Subjects who are discontinued from the clinical trial will not be replaced.

5.3 Subject Withdrawal and Replacement

Subjects may voluntarily withdraw from the clinical trial at any time.

Any female subject will be removed from the clinical trial should pregnancy occur during the course of the clinical trial. The subject will undergo a pregnancy test at the clinical trial exit visit. The pregnancy test must be confirmed by two additional tests and confirmed by the investigator. If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The investigator will document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

Additionally, subjects may be discontinued for safety or sound medical reasons, as determined by the investigator or Sponsor (see Section 5.2).

Reason for withdrawal will be included in the electronic CRF, and all efforts should be made to schedule the subject for a clinical trial exit visit (Visit 4) to complete exit procedures. Any subject withdrawn for the trial because of an AE will be followed until the AE is resolved, or as clinically required. The investigator will prepare a written summary of the event and document the available follow-up information on the electronic CRF.

6 INVESTIGATIONAL TREATMENT

6.1 Description of Investigational Product

[redacted]

6.2 Packaging and Labeling

[redacted]

6.3 Investigational Product Storage

[redacted]

6.4 Investigational Product Accountability

The investigator or designated qualified site staff is responsible for monitoring the inventory of IP and for the accountability of all used and unused IP. Inventories must be carefully and accurately documented according to applicable state, federal, and local regulations, current Good Clinical

Practices (GCPs), including the International Council for Harmonisation (ICH) guidelines, and clinical trial procedures. IP accountability will be verified by the clinical trial monitor during site visits and at the completion of the trial.

The investigator or designated qualified site staff will maintain accurate records of receipt and condition of IP, including dates of receipt. In addition, accurate records will be kept of the date of IP dispensed and the subject to whom IP was dispensed. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

6.5 Investigational Product Retention

IP must be retained until completion or termination of the clinical trial, and written authorization from the Sponsor has been received. All unused and used IP drug should be destroyed at the site or returned to the distributor, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused IP may be disposed until fully accounted for by the clinical trial monitor.

6.6 Investigational Product Administration

IP will be administered by qualified site staff at the designated clinical trial visits (Visits 3 through 4).

6.7 Concomitant Therapy and Procedures

The use of any concomitant medication, prescription or over-the-counter, taken within 30 days prior to Visit 1, is to be recorded on the source document and corresponding electronic CRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical device clinical trial is not permitted.

6.7.1 Prohibited Concurrent Therapies and Procedures

Prohibited medications, treatments, and procedures during the clinical trial are outlined in the Exclusion Criteria (Section 4.2).

7 CLINICAL TRIAL PROCEDURES

Clinical trial assessments and evaluations should be performed by the investigator and/or qualified site staff according to Schedule of Events and Assessments (Table 1). Refer to the Clinical Trial Activities Schedule (Section 8).

7.1 Informed Consent

Informed consent forms must be approved for use by the reviewing Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC). Informed consent must be obtained for all subjects participating in the clinical trial prior to performing any procedures. The informed consent process must be adequately documented in the source records.

7.2 Eligibility Review

The investigator or qualified site staff will confirm that all inclusion and exclusion criteria have been met.

7.3 Demographics, Medical History, and Social History

Demographic information to be captured include date of birth (alternatively year of birth, if full date of birth is not allowed to be collected for legal reasons), age, sex, race, and ethnicity will be obtained from the subject and recorded in the CRF.

Medical and social history will be recorded in the CRF. Current underlying conditions, including conditions diagnosed within the last 30 days of consent, which may have resolved before screening, must be recorded.

7.4 Physical Examination:

A physical examination will be performed including but may not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems at Screening. An oral examination will also be conducted. Additional examinations may be obtained on Investigator's discretion.

7.5 Concomitant Medications

Concomitant medications used 30 days prior to consent to treat any medical conditions will be recorded in the electronic CRF. Any changes in dosage or new medications added must be recorded in the subject electronic CRF. The Sponsor and investigator or qualified site staff will review and evaluate concomitant medication usage on an ongoing basis.

7.6 Adverse Events

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last dose of IP. AEs must be recorded in the electronic CRF. The Sponsor and investigator or qualified site staff will review and evaluate AEs on an ongoing basis. See Section 9 for further detail on AE reporting.

7.7 Vital Signs

Vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, pulse rate, blood pressure (BP), and respiratory rate (RR) prior to EEC entry and at end of Visit 4 prior to study exit.

7.8 Clinical Laboratory Tests

Blood and/or urine samples for standard clinical safety laboratory will be collected at the Medical Screening Visit (Visit 1) and the second Treatment EEC Session (Visit 4) as part of study exit procedures. Samples will be collected at the site by the investigator or qualified site staff.

The investigator must categorize all abnormal laboratory values as either clinically significant or not clinically significant. Clinical significance is defined as any variation in laboratory parameters, which has medical consequences resulting in an alteration in the subject's medical care. In case of clinically significant laboratory results, the investigator will continue to monitor the subject with additional laboratory assessments until values have reached normal range and/or baseline levels. Clinically significant laboratory results should be reported as an adverse event in accordance with Section 9.

7.8.1 Hematology

Hematology profile includes hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, and absolute platelet count.

7.8.2 Chemistry

Serum chemistry profile includes albumin, alkaline phosphatase (ALP), ALT (SGPT), AST (SGOT), BUN, calcium, carbon dioxide (CO_2), chloride, total cholesterol, creatinine, creatinine phosphokinase (CPK), glucose, phosphate, potassium, sodium, total protein, and uric acid.

7.8.3 Pregnancy Test

For WOCBP, a urine pregnancy test will be collected at the Medical Screening Visit (Visit 1), and prior to all EEC Sessions (Visits 2 through 4). Results must be available and confirmed to be negative before the subject may be enrolled in the clinical trial. IP must be discontinued for any subject with a positive pregnancy test result.

7.8.4 COVID-19 Test (SARS-CoV-2 PCR)

Within 5 days of study visits 2, 3, and 4 a nasopharyngeal or oropharyngeal swab will be collected at the clinical site for SARS-CoV-2 PCR testing. Subjects with a positive test result will be excluded/withdrawn from the study.

7.9 Skin Prick Test

A skin prick test for a standard panel of test allergens will be conducted including cat, dust, ragweed, grass or tree pollen. Results must be positive (i.e., a wheal 3 mm greater than the negative control) for at least one test allergen and must include ragweed in order to proceed to the Screening EEC Visit (Visit 2).

7.10 Ophthalmic Examinations

7.10.1 Visual Acuity

VA will be measured using a Snellen eye chart. VA will be measured at the Medical Screening Visit (Visit 1), and pre- and post-entry to the EEC at the Screening and Treatment EEC Sessions (Visits 2 through 4).

7.10.2 Slit Lamp Exam

SLE observations will be graded as “normal” or “abnormal.” Abnormal findings will be categorized as clinically significant (findings that may interfere with trial parameters or otherwise confound the data as determined by the investigator) or not clinically significant. The cornea, conjunctiva, anterior chamber, lens, and eyelid will be examined.

SLE will be conducted at the Medical Screening Visit (Visit 1), and pre- and post-entry to the EEC at the Screening and Treatment EEC Sessions (Visits 2 through 4).

7.10.3 Non-Contact Intraocular Pressure Tonometry (NCT)

Intraocular pressure will be measured using non-contact tonometry. NCT will be measured at the Medical Screening Visit (Visit 1), prior to and post-EEC at the Treatment EEC Sessions (Visits 3 through 4).

7.10.4 Fundoscopy

Dilated or undilated fundoscopy will be performed by the investigator or qualified staff to evaluate for clinically significant fundus abnormalities and vitreous pathology. Fundoscopy will be performed at the Medical Screening Visit (Visit 1), pre-EEC at Visit 2, and post-EEC at the Treatment EEC Sessions (Visits 3 through 4) . Specifically, dilated fundoscopy will be performed at Visit 1 and Visit 4 and undilated fundoscopy will be performed at Visits 2 through 3.

7.11 Symptom Collection

At all EEC sessions (pre- and post-entry), assessments of ophthalmic signs and symptoms will be collected by qualified site staff and subjects [redacted]). In the event of an [redacted] failure, paper diary cards will be used as a back-up to collect symptom scores. Refer to Table 3 and Table 5 for the Schedules of Staff Assessed conjunctival redness and Table 2 and Table 4 for the Schedule of Subject Assessed Itching and Tearing for details on collection time-points.

7.11.1 Staff-Assessed Symptom Collection

At designated time-points, qualified site staff will assess conjunctival redness in each subject using a standard 9-point scale (i.e., 0-4 scale with 0.5 unit increments).

7.11.2 Subject-Reported Symptoms

At designated time-points, subjects will be asked to report and rate symptoms associated with allergic conjunctivitis, including ocular itching, using a standard 9-point scale (i.e., 0-4 scale with 0.5 unit increments). Tearing assessment will be done on a standard 4-point (i.e. 0-3 scale).

7.12 Environmental Exposure Chamber

The EEC clinical research facility is a room designed with the capacity and control mechanisms to expose participants to airborne ragweed pollen grains and maintains target temperature and relative humidity throughout.

[redacted] The controlled pollen challenge, over time, allows evaluation of subject responses at any time-point throughout the challenge process.

[redacted] At the Treatment EEC Sessions (Visits 3 through 4), IP treatment will be administered just prior to EEC entry and approximately 90 minutes post-EEC entry.

7.13 Randomization

After eligibility is confirmed, subjects will be randomized as described in Section 3.2.2.

7.14 Investigational Product Treatment

At Treatment EEC Sessions (Visits 3 through 4), the subject will receive IP according to the treatment sequence the subject was randomized to. The subject will receive one dose of IP just

prior to EEC entry and then another dose will be administered approximately 90 minutes post-EEC entry. IP will be administered by designated site staff only.

Refer to Section 6 for details on IP treatment.

8 CLINICAL TRIAL ACTIVITIES

Clinical trial activities are summarized in the Schedule of Events and Assessments (Table 1)

8.1 COVID-19 Screening

The following procedures will be performed as part of COVID-19 screening:

- Subjects will be pre-screened based upon a COVID-19 questionnaire at each visit;
- Body temperature will be measured at each visit. This measurement may be in addition to other vitals taken at the visit;
- A nasopharyngeal/oropharyngeal swab will be collected for COVID-19 testing within 5 days prior to each EEC session (Visits 2, 3, and 4).
- Most recent COVID-19 test result [redacted] will be reviewed prior to entering the EEC at Visits 2, 3, and 4. Subjects will be allowed to enter the EEC only if COVID-19 test result is negative.

Subject's further participation in the study will be based on the results of the COVID-19 test results and procedures.

8.2 Medical Screening Visit (Visit 1)

- Obtain written informed consent (Section 7.1)
- Review eligibility criteria (Section 7.2)
- Collect demographic information and document medical and social history (Section 7.3)
- Perform physical examination (Section 7.4)
- Collect concomitant medications (Section 7.5)
- Perform VA, SLE, NCT, and dilated fundoscopy (Section 7.10)
- Collect vital signs and samples for laboratory testing (Sections 7.7 and 7.8)
- Collect urine sample for pregnancy test, if applicable (Section 7.8.3)
- Perform skin prick test (Section 7.9)

8.3 Screening EEC Visit (Visit 2)

- Review eligibility criteria (Section 7.2)
- Collect concomitant medications and adverse events (Sections 7.5 and 9)
- Collect vital signs and perform urine pregnancy test (Sections 7.7 and 7.8.3)
- Perform VA and SLE and fundus examination (Section 7.10)

- Obtain symptom collection (staff-assess and subject-reported) pre- and post-EEC entry (Section 7.11)
- [redacted] drop administration just prior to EEC entry
- EEC session (Section 7.12)

8.4 Treatment EEC Session One (Visit 3)

- Review eligibility criteria (Section 7.2)
- Collect concomitant medications and adverse events (Sections 7.5 and 9)
- Collect vital signs (Section 7.7)
- Collect urine sample for pregnancy test (Section 7.8.3)
- Perform VA, SLE, NCT, and undilated fundus exams (Section 7.10)
- Randomization to IP treatment sequence (Section 7.13)
- Obtain symptom collection (staff-assessed and subject-reported) pre- and post-EEC entry per Table 2 and Table 4 and Table 3 and Table 5 (Section 7.11)
- IP treatment (Section 7.14)
- EEC session (Section 7.12)

8.5 Treatment EEC Session Two / Clinical Trial Exit (Visit 4)

- Review eligibility criteria (Section 7.2)
- Collect concomitant medications and adverse events (Sections 7.5 and 9)
- Collect vital signs and samples for laboratory testing (Sections 7.7 and 7.8)
- Collect urine sample for pregnancy test (Section 7.8.3)
- Perform VA, SLE, NCT, and dilated fundus exams (Section 7.10)
- Obtain symptom collection (staff-assessed and subject-reported) pre- and post-EEC entry per Table 2 and Table 4 and Table 3 and Table 5 (Section 7.11)
- IP treatment (Section 7.14)
- EEC session (Section 7.12)
- Clinical trial exit

9 ADVERSE EVENT REPORTING

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last IP administration.

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered an IP, which does not necessarily have a causal relationship with the IP treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IP, whether or not it is considered related to the IP.

Abnormal laboratory and other abnormal investigational findings (i.e., physical exam) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

9.1.1.1 Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the EEC Screening Visit (Visit 2) that do not worsen in severity or frequency during the clinical trial are defined as baseline medical conditions, and are not to be considered AEs.

Pregnancies are not considered AEs but must be reported, see Section 9.1.8.

9.1.1.2 Recording Adverse Events

All AEs must be recorded in the site's clinical trial records and the AE electronic CRF. Investigators should use correct medical terminology when recording events and avoid abbreviations.

The investigator should attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. The diagnosis, and not the individual signs/symptoms, or laboratory abnormalities, should be documented in the subject's source documents and the CRF unless the etiology of the event is unknown. If signs/symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE. If a diagnosis is subsequently established, it should be reported as follow-up information.

An assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to IP, the interventions required to treat it, and the outcome.

9.1.1.3 Assessment of Causality and Severity

For each AE recorded, the investigator will make an assessment of causality and severity as follows:

1. Relationship to IP: The investigator must assess whether they consider an AE to be drug-related. In assessing this relationship, the investigator must use information about the drug as outlined in the Investigator's Brochure, the subject's pre-existent medical conditions/concurrent medication, and chronology of the event relative to drug administration. The following definitions will be used:
   - Definitely Related
   - Probably Related
   - Possibly Related
   - Unlikely to be related
   - Not Related
2. Event Severity: The investigator will be asked to use their medical judgment to assess the severity of the AE.

The following are guidelines to be used by the investigator to judge the event severity of an AE:

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

3. Expectedness: The expectedness of an AE should be determined based on upon existing safety information about the IP using the following explanations:
   - *Unexpected*: an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.
   - *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.
   - *Not applicable:* an AE unrelated to the IP.

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

   The investigator should initially classify the expectedness of an AE, but the final classification is subject to the determination of the Sponsor's Medical Monitor.
4. Duration: Start and end dates and times, or if continuing.
5. Frequency: whether the event is a single episode, recurrent or continuous.
6. Action taken.
7. Whether it constitutes a SAE, per definition below.
8. Outcome: resolved, resolved with sequelae, continuing, death, or unknown (only for subjects that are lost to follow-up).

9.1.2 Treatment-Emergent Adverse Events

A TEAE is defined as an AE that occurred during the clinical trial after the first dose of IP or was present prior to dosing, and exacerbates after the first dose of IP.

9.1.3 Serious Adverse Events

An SAE is any AE that 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/designee, the subject is at immediate risk of death as a result of the AE. "Life threatening" 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; or admission to observation/short stay units, rehabilitation facilities, hospice facilities, nursing homes, or clinical research/Phase 1 units.

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

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

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

- a congenital anomaly/birth defect; and,

- other serious (Important Medical Events) events that do not fit other outcomes, where the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition, based upon appropriate medical judgement.

9.1.4 Unexpected Adverse Events

An unexpected adverse event is defined as an AE, the nature or severity of which is not consistent with the information in the Investigator’s Brochure.

9.1.5 Reporting Serious Adverse Events

The investigator is responsible for reporting all SAEs, regardless of causality, to the Sponsor designee within 24 hours of learning of the occurrence. SAEs should be sent to: [redacted]

(Local toll-free numbers will be provided on the SAE report form cover sheet.)

The reporting timeframe starts when the subject signs the informed consent or assent form through 30 days after the last IP administration. At a minimum, a description of the event and the Investigator’s judgment of causality must be provided at the time of the initial report. These preliminary reports will be followed by detailed descriptions that will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

A follow-up SAE Report must be submitted within 24 hours of the investigator receiving the follow-up information (such as information regarding complications, progression or resolution).

An SAE that is considered completely unrelated to a previously reported event should be reported separately as a new SAE.

The procedures for reporting SAEs are as follows:

- Complete the "Serious Adverse Event Report Form." The investigator may contact Pharmacovigilance via the telephone hotline for assistance with SAE reporting.
- Fax or email the SAE Form to the attention of Pharmacovigilance within 24 hours of the investigator's knowledge of the event.

The original copy of the SAE Report Form and the fax confirmation sheet (or email) must be kept with the source documentation at the clinical trial site.

Follow-up information should be communicated the same way, using a new SAE Report Form stating that it is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from clinical trial participation.

The investigator and qualified site staff should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include clinical laboratory tests not specified in the protocol, histopathologic examinations, or consultations with specialists. The Sponsor or their designee may also request the investigator to conduct supplemental assessments.

If the SAE was not previously documented in the Investigator's Brochure and is thought to be related to IP, the Sponsor or their designee may urgently require further information from the investigator for regulatory authority reporting. The Sponsor may need to issue an investigator Notification to inform all investigators involved in any clinical trial with the same drug that this SAE has been reported.

The investigator should notify Pharmacovigilance of any death or SAE occurring after a subject has withdrawn from the clinical trial when such a death occurs within 30 days of the last dose of IP and may reasonably be related to the IP.

9.1.6 Follow-up of Adverse Events

All AEs will be followed until stabilization/resolution or until clinical database lock.

All SAEs will undergo active follow-up until resolved or the event becomes chronic or stable. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the safety database.

9.1.7 Reporting Serious Adverse Events to Regulatory Health Authorities/ Institutional Review Boards/Research Ethics Boards/Independent Ethics Committees

The investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to their local IRB/REB/IEC.

The investigator must promptly report to his or her local IRB/REB/IEC all unanticipated problems involving risks to subjects. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of IP.

The Sponsor or their designee is responsible for appropriate reporting of relevant AEs, suspected unexpected serious adverse reactions (SUSARs) involving IP, to all regulatory authorities.

In addition, the Sponsor or designee will be responsible for the submission of safety letters (e.g., SUSARs) to the central IRB/REB/IEC and to participating investigators of all SUSARs involving IP according to applicable regulations.

After termination of the clinical trial (determined as last subject, last visit), any unexpected safety issue that changes the risk-benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority (ies) concerned together with proposed actions.

9.1.8 Reporting Pregnancies

Pregnancies will be reported from the time the subject signs the informed consent form through final clinical trial visit or 30 days after the last IP administration, whichever is later.

To ensure subject safety, each pregnancy in a subject on IP must be reported to Pharmacovigilance within 24 hours of learning of its occurrence. Subjects who become pregnant will be withdrawn from the clinical trial. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a subject's source documents and a Pregnancy Notification and Outcome Form and reported by the investigator to Pharmacovigilance using the same procedure for reporting SAEs detailed in Section 9.1.5. A pregnancy, by itself, is not an SAE. Pregnancy follow-up should also be recorded and should include an assessment of the possible relationship to the IP of any pregnancy outcome. Any pregnancy-related SAE (e.g., spontaneous abortion, birth defect) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form and reported per SAE reporting procedures in Section 9.1.5.

10 STATISTICS

10.1 Analysis Populations

The statistical analysis will be based on the analysis populations as defined below:

Safety Population	All randomized subjects who use at least one dose of IP, regardless of whether clinical trial assessments were performed.
Intent-to-Treat (ITT) Population	All randomized subjects who use at least one dose of IP and have any post-dose assessments. Subjects are evaluated according to the IP treatment of the visit as per the randomized treatment sequence.
Per-Protocol (PP) Population	All ITT subjects will be considered PP if IP dosing occurs and do not have a major deviation from the protocol.

[redacted]

10.2 Statistical Hypotheses

The following hypotheses will be tested comparing reproxalap to vehicle in this cross-over design. The null hypotheses must be rejected for the dosing regimen to claim efficacy.

H0: There is no difference between reproxalap and vehicle in the change from baseline in Ocular Itching score on a 9-point scale (0-4) from 110-210 minutes.

H1: The change from baseline in Ocular Itching score on a 9-point scale (0-4) is smaller with reproxalap than with vehicle in the ITT population from 110- 210 minutes.

10.3 Sample Size

Approximately 670 subjects with ragweed-induced, moderate-to-severe allergic conjunctivitis will be screened in the EEC in order to randomize approximately 126 subjects, and for 100 subjects to complete the study. Approximately sixty-three (63) subjects will be assigned to each of two (2) treatment sequences, AB and BA.

[redacted]

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses and will dominate any statistical analysis herein. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc.

10.4 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, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

10.5 Accountability and Background Characteristics

10.5.1 Enrollment and Disposition

The number of subjects enrolled, by study population and investigative site, will be presented by treatment group. The primary reasons for discontinuation will be summarized by treatment and based on the safety population. The number and percentage of subjects with protocol deviations or subjects requiring rescue therapy leading to exclusion from the PP population will be presented by reason for exclusion, stratified by treatment. All deviations and rescued subjects will be listed.

10.5.2 Subject Characteristics

Subject characteristics will be obtained at the Screening prior to randomization and will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation [SD], median, minimum, maximum) and for categorical measures (sample size, frequency and percentages).

Subject characteristics will be summarized on all study populations.

10.5.3 Treatment Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the subjects and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group by means of descriptive statistics (sample size, mean, SD, median, minimum and maximum).

10.6 Primary Efficacy Analysis

The efficacy analyses of all efficacy endpoints will be carried out in the ITT population. Supportive analyses may also be provided for Itching endpoint(s) using the PP population.

Descriptive statistics of all activity endpoints as well as individual data listings will be presented by treatment group and efficacy measures.

For the primary efficacy endpoint, treatment comparisons will be made between Reproxalap Ophthalmic Solution (0.25%) and vehicle. The treatment comparisons will be performed at pre-specified time points (every 10 minutes from 110 minutes to 210 minutes following chamber entry) by using a Mixed Model Repeated Measures(MMRM) approach for a crossover study with two periods.

[redacted]

10.7 Secondary Efficacy Analysis

Secondary efficacy endpoints will be analyzed by using a similar approach as the primary efficacy variable, except over the duration of the chamber (approximately 10 to 210 minutes, as assessed by a single p value for the treatment term. Further details of the analysis plan will be described in statistical analysis plan document (SAP).

10.8 Safety Analysis

Adverse events will be coded using the MedDRA dictionary.

Frequencies and percentages will be provided per treatment group of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation. An adverse event is treatment-emergent if it occurs or worsens after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate analyses will be performed for ocular specific and all adverse events (including systemic).

Other safety endpoints including visual acuity, slit lamp biomicroscopy, intraocular pressure (IOP), tear osmolarity and dilated fundoscopy will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, worst eye (study eye) and fellow eye will be summarized separately.

10.9 Missing Data

[redacted]

[redacted]

10.10 Adjustment for Multiplicity

[redacted]

11 QUALITY CONTROL AND QUALITY ASSURANCE

[redacted] will implement and maintain quality control procedures to insure that the study is conducted, and that the data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

- All participant data relating to the clinical trial will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB//IEC review, and regulatory agency inspections and provide direct/remote access to source data documents.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, written SOPs, study specific plans and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Separate risk management plan will be developed prior to start of the study in accordance with ICH E6 (R2).

The Sponsor may conduct audit visits at clinical study site or remotely to verify adherence to the study protocol, the protection of the rights and well-being of the subjects and the accuracy and completeness of reported study data recorded on the source documentation.

11.1 Pandemic COVID-19 Response Plan

Regulatory authorities have recognized that the Corona Virus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical study. COVID-19 pandemic has created a lot of uncertainty in the current situation and has put subject's safety, protocol compliance and data validity at high risk.

Due to COVID-19 pandemic, challenges may arise for clinical study conduct, for example, quarantines of site personnel/study participants, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with

COVID-19. These challenges may lead to difficulties in meeting protocol specified procedures, including administration or use of investigational product, housing duration or adhering to protocol specified visits and laboratory/diagnostic testing.

To accommodate these challenges and mitigate safety risks associated with COVID-19, changes may be required from approved protocol which include (but not limited to) conducting the study in multiple groups, change in study procedures timing, change in subject's housing duration, additional test or parameter may be performed to standard inclusion or exclusion criteria at the discretion of Investigator/designee, etc. The changes made to the procedure will prioritize subject's safety and data validity and integrity. For any significant change, as per regulatory guidelines, a planned protocol deviation will be filled and notified to IRB and/or local regulatory (as applicable).

All participants will be pre-screened prior to enrolment into the study and evaluated for risk factors and symptoms of COVID-19 according to the most recent regional Public Health guidelines[20] available at the time of pre-screening. The screening is conducted through telephone at the time of appointment confirmation and again when the subject arrives at the clinic for any visit.

Additional health checks including body temperature or other vital sign monitoring, etc. may be performed during the study at the discretion of Investigator/designee, even if not specified in the protocol. Subject who is tested positive to COVID-19 during the study will be withdrawn from the study. This subject and other subjects in close contact will be handled as per applicable local Public Health Guidelines.

As the science and regulations are continuously being adapted to the evolving information around the pandemic, additional measures apart from the ones mentioned here may be undertaken to ensure subject safety and appropriate study conduct. The IRB and the sponsor would be informed for their review and approval as applicable.

Risk Mitigation plan/Risk Evaluation and Mitigation strategy will be made to minimize the risk for COVID-19 exposure and to handle possible situations during COVID-19 pandemic.

12 CLINICAL TRIAL ADMINISTRATION

12.1 Institutional Review Board / Research Ethics Board / Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the investigator and approved in writing by the applicable IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects prior to implementation.

The investigator must provide an annual report to the IRB/REB/IEC on the progress of the clinical trial including number of subjects enrolled, discontinued, and SAEs, unless otherwise specified by the IRB/REB/IEC. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The investigator must provide notification to the IRB/REB/IEC of the completion, termination, or discontinuation of the clinical trial.

The investigator must supply the Sponsor with copies of all written correspondence with the IRB/REB/IEC.

The investigator will make all attempts to ensure that the IRB is constituted and operates in accordance with regulatory requirements, ICH GCP and any local requirements.

12.2 Ethical Conduct of the Clinical Trial

The clinical trial will be carried out in keeping with national and local legal requirements, including in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) Code of Federal Regulations (CFR) Title 21 [Part 50, Part 54, Part 56, Part 312 and Part 11] as well as the ICH GCP E6 Guidelines. This clinical trial was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations [including European Directive 2001/20/EC, US CFR Title 21], and with the ethical principles laid down in the Declaration of Helsinki.

12.3 Subject Informed Consent

The Sponsor will provide sample Informed Consent Forms for use in the clinical trial. Any changes to the proposed consent and assent forms suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/REB/EC. The investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the clinical trial.

Before each subject is enrolled in the clinical trial, written informed consent will be obtained according to the regulatory and legal requirements of the participating site.

The subjects should sign the current final IRB/REC/EC approved consent form. The process of obtaining informed consent and assent should be documented in the subject source documents. Each investigator must retain the original signed and dated informed consent and assent forms. A copy of the signed and dated informed consent and assent forms will be given to the subject. No subject can enter the clinical trial, or have clinical trial-specific assessments performed before his/her informed consent has been obtained.

The Informed Consent Forms should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the patient to participate. Revisions to the consent forms required during the clinical trial must be approved by the Sponsor, and a copy of the revised consent forms provided to the Sponsor. For any updated or revised forms, the subjects must be re-consented for continued participation in the clinical trial.

12.4 Confidentiality

All clinical trial findings and documents will be regarded as confidential. The investigator and qualified site staff must not disclose such information without prior written approval from the Sponsor. The investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified on the CRFs and other documents submitted to the Sponsor by their assigned subject number; not by name. Documents that identify the subject (e.g., the signed informed consent form) must be maintained in confidence by the investigator. All clinical trial documents are provided by the Sponsor in confidence to the investigator and qualified site staff. None of this material may be disclosed to any party not directly involved in the clinical trial without Sponsor's written permission. The investigator must assure that subjects' anonymity will be maintained. The investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

12.5 Protection of Subject Data

The collection and processing of personal data from subjects enrolled in the clinical trial will be limited to those data that are necessary to investigate the safety, quality, and utility of the IP) used in the clinical trial and to support the development and interpretation of the trials clinical outcomes assessments.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the collection and processing of personal data and for the investigator to allow direct access to his or her original medical records for clinical trial-related monitoring, audit(s), IRB/REB/EC review, and regulatory inspection. The consent also addresses the transfer of the data to other entities and to other countries.

12.6 Clinical Trial Monitoring

Prior to initiation of the clinical trial at a site, the Clinical Trial Monitor, who is an authorized individual designated by the Sponsor, will visit the site to verify the qualifications of the investigator and designated site staff, inspect the adequacy of the facilities, and inform the clinical trial team of responsibilities and the procedures to ensure proper conduct of the clinical trial. During the conduct of the clinical trial, the Clinical Trial Monitor will visit the sites to verify adherence to the protocol, assess drug accountability, data integrity, and subject safety. The monitors will conduct 100% source document verification of subject data by comparing the electronic CRFs with the source documents to ensure accuracy and consistency.

All aspects of the clinical trial will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Clinical Trial Monitor will have access to all records necessary to ensure integrity of the data and safety of the subject, and will periodically review the progress of the clinical trial with the investigator.

Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the clinical trial is monitored adequately.

12.7 Case Report Forms and Source Documents

An electronic data capture (EDC) system will serve as the data management system for the clinical trial.

The investigator will be responsible for the accuracy of the data entered in the EDC system and ensure that the data collected are accurate and complete. Data will be monitored within the EDC system by the clinical trial monitor who has only reading rights. Any changes required following monitoring will be made by the investigator or qualified site staff and will be documented with a full audit trail within the EDC system. The responsible clinical trial monitor will check data at the monitoring visits to the clinical site.

The investigator or qualified site staff will prepare and maintain adequate and accurate clinical trial documents (e.g., medical records, AE and concomitant medication reporting, source data collection forms, etc.) designed to record all observations and other pertinent data for each subject. It is recommended that the author of an entry in the source documents be identifiable.

Source data may be directly captured from devices, transferred from third parties (e.g., laboratory data), or entered manually into the EDC system in use at the clinical center. In such case, many of the source data will only be available electronically. The remainder of the data, captured initially on paper, may be entered retrospectively into the EDC system.

For each subject, CRF and corresponding source records will be maintained at each clinical site. CRFs should be completed in a timely manner, and every effort should be made to have forms completed and current in anticipation of a visit by the Sponsor or designee. Upon clinical trial completion, the monitor will arrange for a final review of the clinical trial files, after which the file should be secured by storage for the appropriate period as specified in Section 13.

The investigator will allow the Sponsor or designee(s), contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct/remote access to all documents pertaining to the clinical trial.

12.8 Access to Source Documents and Audits

Regulatory agencies may request access to all clinical trial records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the clinical trial. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the EDC system.

12.9 Protocol Deviations and Violations

Exceptions to the eligibility criteria will not be granted. It is expected that subjects will meet all eligibility criteria. Departures from the protocol should be avoided, unless required for the safety of the subject. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the investigator should contact the Sponsor to discuss the appropriate course of action.

The investigator should document all protocol deviations/violations in the subject's CRF and source documents or the investigator Site File, if appropriate. Protocol deviations will be documented by the clinical trial monitor and will be included in the final clinical trial report. Protocol deviations should be submitted to IRB/REB/IEC, in accordance with the site's IRB/REB/IEC requirements.

12.10 Amendments to the Protocol

To alter the protocol, amendments must be written by the Sponsor and approvals must be received from all parties that approved the original protocol (IRB/REB/IEC, and if applicable, the local regulatory authorities) before implementation. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in the clinical trial, even if this action represents a deviation from the protocol.

The Sponsor may make administrative changes (i.e., changes that do not significantly affect subject safety, the clinical trial's scope or scientific quality) without a formal protocol amendment.

12.11 Discontinuation of the Clinical Trial

The Sponsor reserves the right to discontinue the clinical trial under the conditions specified in the clinical trial agreement.

12.12 Investigator Responsibilities

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IEC/REB/IRB, and/or the regulatory authority(ies).

The investigator is responsible for ensuring that the clinical trial is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and local requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical trial data are credible.

12.13 Financial Disclosure

The investigator is required to disclose any financial arrangement during the clinical trial and for one year after, whereby the outcome of the clinical trial could be influenced by the value of the compensation for conducting the clinical trial, or other payments the investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

12.14 Registration of Clinical Studies and Disclosure of Results

The Sponsor or designee will register and/or disclose the existence of and the results of clinical trials as required by law.

12.15 Publication and Disclosure Policy

As is customary for multicenter trials, publication by individual clinical sites or investigator/institution will not be allowed without the explicit written permission of the Sponsor. The Sponsor will determine authorship of the principal clinical trial manuscript(s) in conjunction with the investigators, in abiding with current guidelines and requirements of medical journals. For such manuscript(s), masthead roles for investigators will be determined based on subject enrollment and scientific contributions to the clinical trial.

13 RETENTION OF RECORDS

The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents, as listed below, must be retained by the investigator for as long as required by national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the clinical trial-related records are no longer required.

Essential documents include but are not limited to:

- IRB/REB/IEC approvals for the clinical trial protocol and all amendments
- All source documents and laboratory records

- CRF copies
- Subjects' informed consent / assent forms (with clinical trial number and title of trial)
- FDA form 1572
- Any other pertinent clinical trial documents

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, IP dispensing/disposition records) that support data in the CRFs of each subject must be retained in the files of the responsible investigator.

According to ICH guidelines for GCP, essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period (25 years) if required by relevant regulatory or legal authorities.

If the responsible investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the clinical trial records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

No records should be disposed of without written approval of the Sponsor.

14 REFERENCES

[redacted]