

CLINICAL PROTOCOL

CO-161103095739-VCCT

A Single-Center, Randomized, Controlled Study to Evaluate the Efficacy of Two Investigational OTC Eye Drops in Healthy Adults with Red Eye

Investigational Product Name:	██████████
Protocol Number:	CO-161103095739-VCCT
IND / IDE / EudraCT number:	N/A
Phase:	III
Version Date	Protocol Final Draft Version: 28MAR2017

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1. SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Consumer Inc. (JJCI)
Active Ingredient(s): <u>Investigational Product #1 - [REDACTED] Eye Drops:</u> Tetrahydrozoline 0.05%; Glycerin 0.40% (F# 13418-148) <u>Investigational Product #2 - [REDACTED] Eye Drops:</u> Tetrahydrozoline 0.05%; Glycerin 0.20%, Hypromellose 0.2%, Polyethylene glycol 400 1.0% (F# 13418-158), <u>Positive Control:</u> [REDACTED], Tetrahydrozoline 0.05%, (F# PF-004390 UPC #74300008035)
Title of Study: A Single-Center, Randomized, Controlled Study to Evaluate the Efficacy of Two Investigational OTC Eye Drops in Healthy Adults with Red Eye
Countries: United States
Principal Investigator/Site: [REDACTED] Andover Eye Associates 300 Brickstone Square Andover, MA 01810
Phase of development: III
Objectives: The objective of this study is to demonstrate the therapeutic equivalence of two investigational, over-the-counter (OTC) redness reliever eye drop formulations to an existing marketed OTC redness reliever eye drop in healthy adults with red eye.
Methodology: <p>This is a 3-arm, single center, double-blinded, balanced incomplete randomized block design study. Subjects will undergo a 1-day (3 doses over 9 hours total) intervention period where each subject will be randomly assigned to receive 2 of the 3 test products to apply to the left and right eyes. For the duration of the study, subjects will be asked to refrain from using all eye treatments, including contact lenses.</p> <p>Eligible subjects will complete 2 clinic visits. All subjects will have an ocular health and vision exam for inclusion in the study during clinic Visit 1. Eligible subjects will have ocular redness assessments using a 5- point redness scale at Baseline (pre-treatment prior to 1st product application), and then 30 seconds, 60 seconds, and 2 minutes following the 1st product application. Subjects will also complete ocular comfort assessments for each eye using a scale of 0 to 10 at Baseline (pre-treatment prior to 1st product application) and immediately following the Ocular Redness Assessment completed at 60 seconds after the 1st product application. The first dose will be instilled by trained study staff at the clinic. Subjects will also complete a questionnaire at Baseline (pre-treatment prior to 1st product application) and immediately following the 2- minute Ocular Redness Assessment. Subjects will be provided product and</p>

written and verbal instructions to apply the test product at home. Subjects will apply test products at home at 4.5 hours (\pm 30 minutes) and 9 (\pm 30 minutes) hours after the 1st product application in the clinic. They will also complete an Ocular Comfort Assessment and questionnaire at 10 hours (+ 15 minutes) and 12 hours (+ 15 minutes) at home.

Subjects will return in approximately 24 ± 1 hour(s) for a final vision exam.

Number of subjects (planned):

Randomize 120 subjects to complete with 114 subjects

Diagnosis and main criteria for inclusion:

General Inclusion Criteria:

1. Able and willing to comprehend and follow the requirements of the study (including availability on scheduled visit dates) based upon research site personnel's assessment;
2. Able and willing to provide a signed and dated Informed Consent document and Authorization for the Release of Health Information for Research
3. Male or female of any race or ethnicity, aged 18 years and older;
4. Females of childbearing potential who have a negative urine pregnancy test at the Screening/Baseline visit (Visit 1);
5. Able to read and understand the local language;
6. Healthy subjects presenting in office with bilateral, mild/moderate ocular redness [REDACTED];
7. History of topical ocular vasoconstrictor use or a desire to use topical OTC vasoconstrictors for eye redness relief within the last 6 months;
8. Ocular health within normal limits, in the judgement of the medically qualified investigator, including visual acuity of [REDACTED] or better in each eye [as measured using Early Treatment Diabetic Retinopathy Study (ETDRS) chart]] at Visit 1;
9. Male and female subjects with reproductive potential who agree to practice a medically acceptable form of birth control (described in section 10.7.4) during the study and for 30 days following the last dose of investigational product. Females must have used such birth control for at least 3 months prior to the Screening/Baseline Visit 1.

Subject Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Suspected alcohol or substance abuse (e.g., amphetamines, benzodiazepines, cocaine, marijuana, opiates);
2. Known sensitivity, allergy or contraindications to any investigational product ingredient;

3. Females who are pregnant, planning to become pregnant or breastfeeding during the study;
4. Subjects who were previously screened and determined to be ineligible for the study;
5. Use of a therapeutic eye treatment (over-the-counter or prescription) within 2 days of the Screening/Baseline visit (Visit 1) and throughout study participation;
6. Participation in any clinical study investigation within 30 days of Screening/Baseline visit (Visit 1);
7. Relative, partner or staff of any clinical research site personnel;
8. Active infection of any type at the start of the study; particularly, presence of active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection;
9. Any ocular condition that could affect the subject's safety or trial parameter, such as severe ocular allergy;
10. Planned surgery during the trial period, 6 months prior to clinic visit 1 or 30 days after the end of study period;
11. Has a compromised immune system;
12. Has any acute or chronic, medical or psychiatric conditions) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgement of the medically qualified investigator, would make the subject inappropriate for entry in this study;
13. Contact lens use within 24 hours prior to clinic Visit 1 and during their participation in the study;
14. Saline eye drop use within 24 hours prior to clinic Visit 1 and during their participation in the study;
15. Use of any new OTC or prescription medications within 24 hours prior to clinic Visit 1 and throughout study participation.

If the subject reports taking medication, a history of allergy, and/or a chronic disease which in the opinion of the investigator will not affect the clinical parameter(s) being assessed in this study or the safety of the subject, the subject may be enrolled in the study and it will be noted on the Investigator's source document.

Study product, dosage and mode of administration:

Investigational Product #1: Tetrahydrozoline 0.05%; Glycerin 0.40% (F# 13418-148), 1-2 drops in the assigned eye every 4.5 hours (3 doses total), topical application

Investigational Product #2: Tetrahydrozoline 0.05%; Glycerin 0.20%, Hypromellose 0.2%, Polyethylene glycol 400 1.0% (F# 13418-158), 1-2 drops in the assigned eye every 4.5 hours (3 doses total), topical application

Reference therapy (comparator or placebo control), dosage and mode of administration:

Positive Control: [REDACTED], Tetrahydrozoline 0.05%, (F# PF-004390, UPC #74300008035), 1-2 drops in the assigned eye every 4.5 hours (3 doses total), topical application

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Duration of treatment: 1 Day (3 doses over 9 hours)

Data for evaluation:

Efficacy:

The efficacy measurements include clinician assessment of redness, [REDACTED]
[REDACTED]

Primary endpoint:

- Change from baseline in redness at 60 seconds after the first application.

Secondary endpoints:

- Change from baseline in redness at 30 seconds after first product application.
- Change from baseline in redness at 2 minutes after first product application.
- Change from baseline in ocular comfort at approximately 60 seconds, 10 hours (+ 15 minutes) and 12 hours (+ 15 minutes) after first application.
- Subject questionnaire frequency tabulations at baseline, approximately 2 minutes, 10 hours (+ 15 minutes) and 12 hours (+15 minutes) after first product application

Safety:

Ocular vision exams will be completed at baseline and also approximately 24 hours after first product application.

Safety will be monitored and assessed by the collection, evaluation, and analysis of adverse events (AEs).

Statistical methods:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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2. STUDY FLOW CHART AND SCHEDULE OF ACTIVITIES

	Visit 1 Screening/Baseline	Home	Visit 2/ End of Study 24 hours \pm 1 Hour
Obtain Informed Consent and Authorization for the Release of Health Information for Research	X		
Collect Medical History and Demographics	X		
Prior and Concomitant Medications/ Non-Drug Therapies	X		
Review Inclusion/Exclusion Criteria	X		
Urine Pregnancy Testing on women of childbearing potential	X		
Baseline Subject Ocular Comfort Assessment and Subject Questionnaire (Pre-treatment)	X		
Vision/Eye Examination (see protocol for details)	X		X ¹
Baseline Ocular Redness Assessment (Pre-treatment) & eligibility determination based on redness by Clinician	X		
Randomization	X		
Product Application in clinic by trained staff and at home by subjects	X	X	
Ocular Redness Assessment by clinician after 1 st product application at 30 and 60 seconds, and at 2 minutes	X		
Subject Ocular Comfort Assessment, immediately following the 60 second Ocular Redness Assessment and by subject at home at 10 and 12 hours (+ 15 minutes) after first application	X	X	
Subject Questionnaire, immediately following the 2-minute Ocular Redness Assessment and by subject at home at 10 and 12 hours (+15 minutes) after first application	X	X	
Dispense Product, Diary, verbal and written instructions for Use, Home Questionnaires	X		
Adverse Event Assessment	X	X	X
Collect Product, Review Diary & Home Questionnaires			X
Subject Disposition	X		X

¹ Only Visual Acuity Completed at Visit 2

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE(s)	Adverse Event(s)
BAK	Benzalkonium chloride
CRF	Case Report Form
DPR	Designated Physician Representative
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food & Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
OTC	Over-the -counter
PI	Principal Investigator
PQC	Product Quality Complaint
SAE	Serious Adverse Event

4. ETHICS

4.1. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator Site Master File (SMF). Copies of IRB/IEC approvals should be forwarded to the Sponsor.

The only circumstance in which a protocol amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and the Sponsor in writing within 5 working days after implementation.

4.2. Ethical Conduct of the Study

The study will be performed in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice guidelines (ICH E6) and applicable local regulatory requirements and laws.

4.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or subject initials on any forms, reports, publications, or in any other disclosures. Each subject will be assigned a subject ID number that is used in the Case Report Form (CRF) in lieu of the subject's name. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by the Sponsor and the IRB/IEC and must be in compliance with current ICH E6, Good Clinical Practices, local regulatory requirements, and legal requirements and be in a language that the subject can read and understand.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before use. The Investigator will retain the original of each subject's signed consent form. A copy of the signed and dated consent form will be provided to subjects.

Only subjects who provide informed consent will enter in the study.

5. STUDY ADMINISTRATIVE STRUCTURE

Details on the administrative structure of the study (e.g., Principal Investigator (PI)/study site personnel, the Sponsor's study team, and the external service providers) will be included in the study contact list. The study contact list will also include contact information for the Sponsor, Investigator(s), Monitor(s), and IRB(s), as well as the names and titles of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor. This list will be maintained in the trial and site master files throughout the study for inclusion in the Trial Master File.

6. INTRODUCTION

Red eye is a common ophthalmologic condition and can include almost any part of the eye.¹ Conjunctival hyperaemia is caused by vasodilation of the conjunctival blood vessels in response to irritation. This vasodilation causes the red appearance of the normally white appearing sclera, leading to the condition commonly known as “red eye”.³ Red eye is treatable with over-the-counter (OTC) medications.²

Preservatives like benzalkonium chloride (BAK) have come under the scrutiny of research studies over the years for their potential to disrupt the protective tear film and ocular surface cells. The medical community has deemed that despite its efficient bactericidal qualities, BAK is more cytotoxic in high quantities than many other preservatives. In order to provide an alternative to BAK, this study will be conducted to test the efficacy of two new investigational products containing, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7. STUDY OBJECTIVES AND ENDPOINTS

The objective of this study is to demonstrate the therapeutic equivalence of two investigational, over-the-counter (OTC) redness reliever eye drop formulations to an existing marketed OTC redness reliever eye drop in healthy adults with red eye.

The efficacy measurements include clinician assessment of redness, [REDACTED]

[REDACTED] A subject questionnaire is also being administered to evaluate consumer sensory benefits.

Primary endpoint:

- Change from baseline in redness at 60 seconds after the first application.

Secondary endpoints:

- Change from baseline in redness at 30 seconds after first product application.
- Change from baseline in redness at 2 minutes after first product application.
- Change from baseline in ocular comfort at approximately 60 seconds, 10 hours (+ 15 minutes) and 12 hours (+ 15 minutes) after first application.
- Subject questionnaire frequency tabulations at baseline, approximately 2 minutes, 10 hours (+15 minutes) and 12 hours (+15 minutes) after first product application

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design and Plan

This is a 3-arm, single center, double-blinded, balanced incomplete randomized block design study. Subjects will undergo a 1-day (3 doses over 9 hours total) intervention period where each subject will be randomly assigned to receive 2 of the 3 test products to apply to the left and right eyes. For the duration of the study, subjects will be asked to refrain from using all eye treatments, including contact lenses.

Eligible subjects will complete 2 clinic visits. All subjects will have an ocular health and vision exam for inclusion in the study during clinic Visit 1. Eligible subjects will have ocular redness assessments using a 5- point redness scale at Baseline (pre-treatment prior to 1st product application), and then 30 seconds, 60 seconds, and 2 minutes following 1st product application. Subjects will also complete Ocular Comfort Assessment for each eye using a scale of 0 to 10 at Baseline (pre-treatment prior to 1st product application) and immediately following the Ocular Redness Assessment completed 60 seconds after the 1st product application. The first dose will be instilled by trained study staff at the clinic. Subjects will also complete a questionnaire at Baseline (pre-treatment prior to 1st product application) and immediately following the 2- minute Ocular Redness Assessment. Subjects will be provided product and written and verbal instructions to apply the test product at home. Subjects will apply test products at home at 4.5 hours (\pm 30 minutes) and 9 (\pm 30 minutes) hours after the 1st product application in the clinic. They will also complete an Ocular Comfort Assessment and questionnaire at 10 hours (+ 15 minutes) and 12 hours (+15 minutes) at home.

Subjects will return in approximately 24 ± 1 hour(s) for a final vision exam.

8.2. Criteria for Subject Termination

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, product safety problems or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue the study at any time.

8.3. Subject Inclusion / Exclusion Criteria

8.3.1. Subject Inclusion Criteria

This clinical study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. No waivers to inclusion or exclusion criteria will be permitted.

Subjects must meet all of the following inclusion criteria (and none of the exclusion criteria) to be eligible for enrollment into this study:

General Inclusion Criteria

1. Able and willing to comprehend and follow the requirements of the study (including availability on scheduled visit dates) based upon research site personnel's assessment;
2. Able and willing to provide a signed and dated Informed Consent document and Authorization for the Release of Health Information for Research;
3. Male or female of any race or ethnicity, aged 18 years and older;
4. Females of childbearing potential who have a negative urine pregnancy test at the Screening/Baseline visit (Visit 1);
5. Able to read and understand the local language;
6. Healthy subjects presenting in office with bilateral, mild/moderate ocular redness [REDACTED]
7. History of topical ocular vasoconstrictor use or a desire to use topical ocular OTC vasoconstrictors for redness relief within the last 6 months;
8. Ocular health within normal limits, in the judgement of the medically qualified investigator, including visual acuity of [REDACTED] or better in each eye [as measured using Early Treatment Diabetic Retinopathy Study (ETDRS) chart] at Visit 1;
9. Male and female subjects with reproductive potential who agree to practice a medically acceptable form of birth control (described in section 10.7.4) during the study and for 30 days following the last dose of investigational product. Females must have used such birth control for at least 3 months prior to the Screening/Baseline visit.

8.3.2. Subject Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Suspected alcohol or substance abuse (e.g., amphetamines, benzodiazepines, cocaine, marijuana, opiates);
2. Known sensitivity, allergy or contraindications to any investigational product ingredient;
3. Females who are pregnant, planning to become pregnant or breastfeeding during the study;
4. Subjects who were previously screened and determined to be ineligible for the study;
5. Use of a therapeutic eye treatment (over-the-counter or prescription) within 2 days of the Screening/Baseline visit (Visit 1) and throughout study participation;
6. Participation in any clinical study investigation within 30 days of Screening/Baseline visit (Visit 1);
7. Relative, partner or staff of any clinical research site personnel;
8. Active infection of any type at the start of the study; particularly, presence of active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection;
9. Any ocular condition that could affect the subject's safety or trial parameter, such as severe ocular allergy;

10. Planned surgery during the trial period, or 6 months prior to clinic visit 1 or 30 days after the end of study period;
11. Has a compromised immune system;
12. Has any acute or chronic, medical or psychiatric conditions) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgement of the medically qualified investigator, would make the subject inappropriate for entry in this study;
13. Contact lens use within 24 hours prior to clinic Visit 1 and during their participation in the study;
14. Saline eye drop use within 24 hours prior to clinic Visit 1 and during their participation in the study;
15. Use of any new OTC or prescription medications within 24 hours prior to clinic Visit 1 and throughout study participation.

If the subject reports taking medication, a history of allergy, and/or a chronic disease which in the opinion of the investigator will not affect the clinical parameter(s) being assessed in this study or the safety of the subject, the subject may be enrolled in the study and it will be noted on the Investigator's source document.

8.3.3. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason without compromising their rights to receive further treatment. The Investigator and/or the Sponsor may terminate a subject from investigational treatment and/or study follow-up in the event of any of the following:

- Medical reasons considered significant by the subject, Investigator and/or the Sponsor, which may include, an adverse event, inter-current illness or medical reasons unrelated to the study
- Nonmedical reasons (e.g., subject request or noncompliance with the treatment procedure as determined by the investigator, the Sponsor and/or subject)
- Pregnancy
- Serious eligibility or on-study violation of the protocol
- Administrative or other reasons

Should a subject decide to withdraw from the study at any point, all efforts should be made to complete all end of study assessments (if subject cannot come to study site, a telephone call to collect information could be performed). In case of questions surrounding the circumstances that a subject needs to be withdrawn from the study (e.g., protocol deviation), the Sponsor, or the Sponsor representative should be consulted. The reason for withdrawal should be documented in the subject's source document and on the Subject Disposition EDC page.

If a subject does not return for a scheduled visit, three documented attempts will be made to contact the subject via:

1. Documented phone call (date, time, person completing the call, result)
2. Regular mail

3. Certified letter/return receipt (if service is available)

The site should request the subject return all used/unused investigational product(s), and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Description of Investigational Products

Table 2: Investigational Products

Investigational Product # 1 [REDACTED] Eye Drops	Tetrahydrozoline 0.05%; Glycerin 0.40%
Dosage Form	Eye Drops
Formula Number	(F# 13418-148)
Route of Administration	ocular
Physical Description	Clear liquid
Manufacturer	Johnson & Johnson Consumer Inc.
Investigational Product #2 [REDACTED] Eye Drops	Tetrahydrozoline 0.05%; Glycerin 0.20%, Hypromellose 0.2%, Polyethylene glycol 400 1.0%
Dosage Form	Eye Drops
Formula Number	(F# 13418-158)
Route of Administration	ocular
Physical Description	Clear liquid
Manufacturer	Johnson & Johnson Consumer Inc.

Table 3: Investigational Control Product

Positive Control	[REDACTED], Tetrahydrozoline 0.05%; UPC #74300008035
Dosage Form	Eye Drops
Formula Number	(F# PF-004390)
Route of Administration	ocular
Physical Description	Clear liquid
Manufacturer	Johnson & Johnson Consumer Inc.

9.2. Investigational Product Packaging and Labeling

All three products will be identical in color. Test products will be provided in randomization number specific kits, utilizing a one-part label containing the following information:

- Protocol Number
- Randomization Number
- Right Eye or Left Eye
- Site Identification
- 24-Hour Emergency Phone Number
- Directions for Use
- For Investigational Use
- Warnings
- Net Contents
- Expiration
- Storage Conditions

Labeling of study supplies will be in compliance with applicable regulatory requirements. All investigational, including any commercially available, must be stored in accordance with the manufacturers' instructions. Investigational product supplies must be stored separately. Until dispensed to the subjects, the investigational product will be stored in a securely locked area, only accessible to authorized personnel.

9.3. Blinding and Unblinding

The Sponsor will provide blinded investigational product. The Investigator/Clinician and the subjects will not have access to the treatment code.

The Investigator/Clinician will not know which treatment has been administered to subjects. Personnel dispensing the test products, collecting used products or supervising their use will not participate in the examination of subjects in order to minimize potential bias. During supervised use, other staff members including the Investigator/Clinician will not have access to the area where the product is being administered.

The randomization scheme will be used by the Clinical and Consumer Packaging Operations Department to generate the subject specific single disclosure envelopes. The site clinical study coordinator will receive one package containing individual subject specific disclosure envelopes indicating treatment decode for each randomization number. Identification of the products assigned to a subject may be revealed in the event of a serious adverse event by opening the single subject specific envelope that displays the subject's randomization number. In such an instance, the Investigator will, if circumstances and time permit, contact the Sponsor prior to breaking the code. The date and reason for

such unblinding must be described on the subject's source document. Upon completion of the study, all subject specific disclosure envelopes must be returned to the study monitor who will return them to the sponsor.

Blinding should only be broken when required and only for the subject in question. The Investigator must notify the Sponsor, when circumstances and time permit, prior to unblinding of any subject. Expectedness of serious and related adverse events should be assessed using the Safety Attestation letter and/or, for marketed products, the locally approved labeling.

If there is a medical emergency and the Investigator deems it necessary to know the subject's study treatment urgently for the subject's proper medical care, the Investigator may break the treatment code immediately, and then contact the Study Director or designee as soon as possible afterward. If in the opinion of the Investigator it is necessary to break the treatment code and circumstances allow, the Investigator will first contact the Study Director or designee for consultation about breaking the study blind.

9.4. Method of Assigning Subjects to Treatment Groups

As the subjects sign a consent form, (s)he will be sequentially issued a subject ID. The subject ID will begin with the center ID "1001" followed by a four- digit unique subject identifier, e.g. "10011001". Upon qualifying, a unique randomization number will be assigned. This number determines the treatment sequence assignment for each subject according to a randomization schedule. Each subject will be randomized to receive 2 of the 3 Investigational Products, one for each eye. Both products will be packaged in individual subject kits. The product labels will clearly state "LEFT EYE" or "RIGHT EYE". The randomization will be assigned sequentially, from 1-120. Once a randomization number has been assigned to a subject, it cannot be reassigned to another subject. The treatment sequence assignments of the investigational product and control will be based on a randomization scheme devised by the Sponsor. The randomization scheme will be used by the Sponsor to generate the randomization-number-specific single disclosure envelopes.

9.5. Study Product Storage and Accountability

The Investigator, or a designated study staff, will ensure that all investigational products are stored in a secured area at room temperature and in accordance with applicable regulatory requirements. Until dispensed, the investigational product will be stored in a securely locked area, accessible only to authorized personnel.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product on the Investigational Product Accountability Log supplied by the Sponsor or Designee. The log must identify the investigational product and account for its disposition on a subject-by-subject basis, including specific dates and quantities dispensed and returned. The log must be signed by the individual who dispensed/retrieved the study product, and copies must be provided to the Sponsor at the end of the study for the Trial Master File.

At the end of the study, the Study Monitor will conduct the final investigational product accountability. All investigational products and study disclosure envelopes must be returned to the Sponsor. The Sponsor will provide instructions as to return of any used and unused investigational product.

9.6. Administration of the Investigational Product

Subjects will be provided written and oral instructions for their products by the site.

9.7. Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability or safety of a product, including its labeling, delivery system or packaging integrity. This does not include effectiveness, preference or performance measures, which will be reviewed in aggregate at appropriate intervals.

Any issues with the product discovered during the initial inventory of study supplies should follow the instructions provided on the receipt letter; no PQC form should be filed for issues identified when opening or unpacking a shipment. Subsequently, any observation of a PQC requires immediate notification to the study manager via a completed PQC form and telephone call.

The PI or designee should complete, sign and forward a copy of the PQC form, via an agreed upon secure exchange, to the study manager listed below.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In addition, PQC information must be included on the Investigational Product Dispensing and Accountability Log or equivalent in the comments field. The Study Manager listed can assist you or answer questions related to this process. To aid in the initial conversation and understanding of a PQC, the site staff may be asked to photograph the issue and send it to the Study Manager.

When enrolling subjects into this study it is the site's responsibility to instruct subjects not to use the product if they have a concern related to the product such as an issue with the labeling, investigational product or package integrity and to immediately report it using the instruction on the Informed Consent or product label.

10. STUDY PROCEDURES

10.1. Overview

Collection of adverse events and concomitant medications will start after the study-specific informed consent document has been signed and continue until completion of the follow-up/end of study procedures. The Schedule of Activities/Study Flow Chart (Table 1) summarizes dose administration and the timing and frequency of safety and efficacy procedures and measurements. In the event of abnormal safety findings during the conduct of the study, the attending clinician may request additional safety evaluations, either immediately or subsequently at a frequency considered appropriate.

10.2. Visit 1 (Day 1) – Screening/Baseline

Informed consent will be obtained from the subjects before any study related assessments are conducted. Trained study staff will complete the following activities for each subject:

- Obtain written Informed Consent and Authorization for the Release of Health Information for Research;
- Collect demography
- Collect significant medical history within one year, e.g., major medical conditions
- Collect history of prior (past 30 days) and concomitant medications and non-drug therapy
- A urine pregnancy test (dipstick) will be completed on all women of child bearing potential
- Pre-treatment Baseline Subject Ocular Comfort Assessment will be evaluated using a Scale [REDACTED]
- Pre-treatment Baseline Subject questionnaire will be completed;
- Perform vision/ eye examination. The following procedures will be performed:
 - Visual Acuity
 - Slit lamp biomicroscopy
- Pre-treatment Baseline ocular redness will be assessed by a trained clinician;
- Review inclusion exclusion criteria;
- Randomization;
- The first dose of each Investigational product will be instilled in the clinic by trained study staff;
- Investigational products will be instilled in each eye, and then the assessments described below will begin;
- Ocular redness will be assessed at 30 seconds, 60 seconds and 2 minutes after product application;
- Subject Ocular Comfort Assessment will be evaluated immediately following the 60 second Ocular Redness Assessment (and before the 2-minute Ocular Redness Assessment) using a scale [REDACTED];

- A Post-treatment subject questionnaire will be administered immediately following the 2-minute Ocular Redness Assessment;
- Investigational products, instructions for use, diary and questionnaires will be dispensed to the subjects for the home use;
- Verbal and written instructions will be provided for subject home use. Subjects will be instructed to apply 1-2 drops of each test product in the designated eye two more times on the same day as clinic visit 1, at 4.5 hours (\pm 30 minutes) and 9 (\pm 30 minutes) after the first dose applied at the clinic. They will also complete subject questionnaires and ocular comfort assessments at home at 10 hours (+ 15 minutes) and 12 hours (+ 15 minutes);
- Visit 2 appointment will be scheduled;
- Adverse events will be assessed

10.3. Visit 2 (24 hrs \pm 1 hr) End of Study

- Update any changes in medical history or concomitant medications and non-drug therapies;
- Assess for adverse events since last visit;
- Collect investigational products, collect and review diaries and questionnaires;
- Complete final vision/eye exam. This exam will consist of only a Visual Acuity assessment;
- Complete Subject Disposition/Exit

10.4. Randomization

Subjects who meet the eligibility criteria, will be randomized during Visit 1. The Sponsor will be responsible for the generation of the randomization schedule and products will be packaged in individual subject kits according to this randomization schedule.

10.5. End of Study Procedures

End of study is defined as the subject's last day of study participation due to study completion or early withdrawal/termination. Assessment of adverse events, collection of study materials and subject disposition should be completed.

10.6. Unscheduled Follow Up Visit(s)

If a subject experiences an adverse event that is deemed to have a causal relationship to the trial procedures, when the subject either completes or discontinues participation in the study, he/she must return to the site for a follow-up visit and should be followed until the adverse event resolves.

10.7. Life Style Guidelines

10.7.1. Meals and Dietary Restrictions

All subjects will be asked to maintain their normal dietary habits throughout this study.

10.7.2. Alcohol, Caffeine and Tobacco Consumption / Restrictions

There is no alcohol, caffeine or tobacco limits or restrictions placed on subjects who choose to participate in this study.

10.7.3. Physical Activity Requirements / Restrictions

There are no physical activity requirements or restrictions for subjects who choose to participate in this study.

10.7.4. Contraception for Females

Male and female subjects with reproductive potential must agree to practice a medically acceptable form of birth control during the study and for 30 days following the last dose of investigational product whichever is later. Females must have used such birth control for at least 3 months prior to the Screening/Baseline visit.

Medically acceptable forms of birth control that may be used by the subject and/or his/her partner include:

- Established use of hormonal methods of contraception (oral, injected, implanted, patch or vaginal ring)
- Barrier methods of contraception with spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/ film/ cream/ suppository.
- Intrauterine device (IUD) or intrauterine system (IUS)
- Surgical sterilization (e.g., vasectomy that has been confirmed effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy)
- Abstinence from heterosexual intercourse: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

A female subject who is postmenopausal (i.e., amenorrheic for at least 12 months prior to the Screening/Baseline visit) is not considered of reproductive potential.

10.8. Treatment Compliance

Each subject will record at-home eye drop use on the subject diary. Study personnel will review the subject diary at the next clinic visit to ensure subject was compliant with the instructions. Any deviations from the study requirements will be recorded on the deviation log.

10.9. Previous and Concomitant Medications

Medications or non-drug therapies used 30 days before the Screening visit and during the study will be recorded in the source document.

Any medication the subject takes other than the investigational product specified in the protocol is considered concomitant medication.

10.10. Rescue Therapy

No rescue therapy is provided for in this protocol.

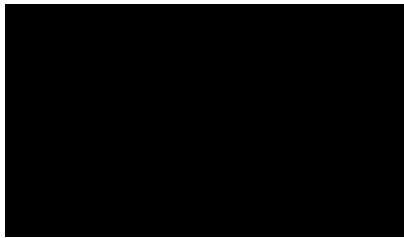
11. ASSESSMENTS

11.1. Efficacy Measurements and Evaluations

The efficacy measurements include clinician assessment of ocular redness, subject reported ocular comfort and subject questionnaire.

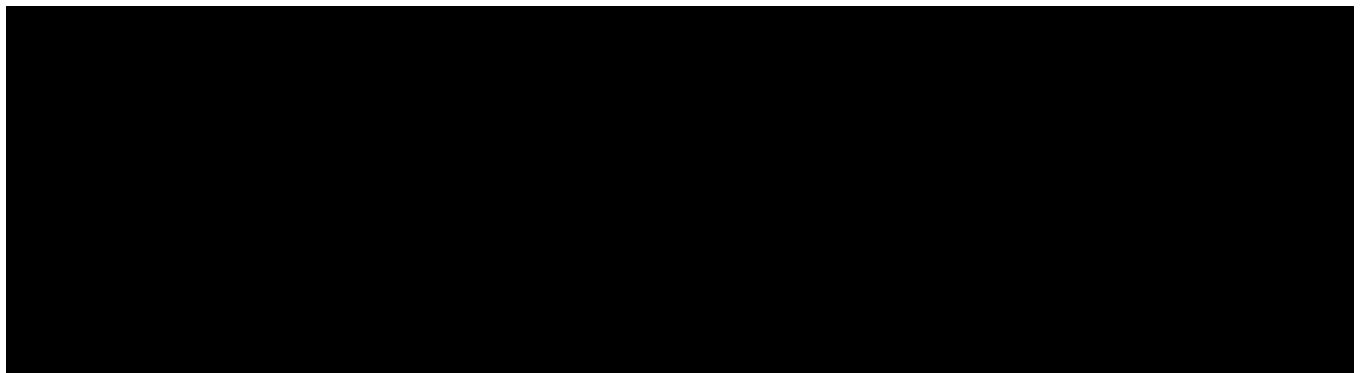
11.1.1. Clinician Ocular Redness Assessment

The clinical assessment of redness will use a [REDACTED]
[REDACTED]. Redness will be evaluated in each eye at baseline (pre-treatment prior to 1st product application) and then 30 seconds, 60 seconds, and 2 minutes after the 1st product application. [REDACTED]



11.1.2. Subject Ocular Comfort Assessment

The subject reported Ocular Comfort Assessment will be evaluated in each eye using a scale [REDACTED] at baseline (pre-treatment prior to 1st product application) and immediately following the 60 second Ocular Redness Assessment after 1st product application (and before the 2-minute Ocular Redness Assessment), and then from home at 10 hours (+15 minutes) and 12 hours (+ 15 minutes) after the 1st product application. Increments of 0.5 are not permitted. Subjects will be shown the scale and asked to select the point on the scale that corresponds to their comfort level. The Ocular Comfort scale is included below:



- 11.1.3.** A subject questionnaire will be completed at Baseline (pre-treatment), and post-treatment after the 2-minute ocular redness assessment in-clinic, and at home at 10 hours (+15 minutes) and 12 hours (+ 15 minutes) after the 1st product application.

11.2. Ocular Safety Assessments

Ocular vision exams will be completed at screening (visual acuity and slit lamp biomicroscopy) and also approximately 24 hours after 1st product application (visual acuity only).

Safety will be monitored and assessed by the collection, evaluation, and analysis of subject reported spontaneous adverse events (AEs). If an AE is reported, the subject will be asked to elaborate on the nature of the event. The Investigator or designated clinician will evaluate and record according to the Adverse Event Reporting section (Section 12) of the protocol.

Any clinically important abnormalities or causally-related AEs persisting will be followed by the Investigator until resolution or until reaching a clinically stable endpoint. AEs will be reported by the subject for the duration of the study, beginning with the signing of the study specific informed consent. AEs will be followed by the Investigator as specified in Section 12, Adverse Event Reporting.

A clinically significant visual acuity decrease (defined as an increase of [REDACTED] or greater in logMAR score) from baseline (Visit 1) will be considered an Adverse Event. logMAR scores will be recorded in the source document.

12. ADVERSE EVENT REPORTING

12.1. Introduction

All observed or volunteered AEs regardless of treatment group, or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. For all AEs, the Investigator or medically qualified individual (MD/DO/DMD/DDS) must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) requiring immediate notification (within 24 hours) to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator or medically qualified individual (MD/DO/ DMD/DDS) to try to determine causality. The Investigator is required to assess causality. For AEs with a suspected causal relationship to the investigational product, follow-up by the Investigator or medically qualified individual (MD/DO/ DMD/DDS) is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and the Sponsor concurs with that assessment.

12.2. Reporting Period

All AEs, whether serious or non-serious, observed and/or spontaneously reported, beginning from the time the informed consent is signed and dated, are collected on the source document. AEs of randomized subjects will be reported in EDC while screen failure subjects will not. Informed consent is considered the point at which the subject is participating in the clinical study and all events are captured even if it is prior to undergoing any study-related procedure and/or receiving investigational product. Non-serious adverse events will be reported through the subject's last study visit (or termination if the subject terminates early from the study for any reason). Non-serious adverse events are to be reported in the source documents and the adverse event page of the EDC. Details of any signs and symptoms will be described and recorded, including resolution of the adverse event.

Spontaneous reports of serious AEs will be collected through and including 30 calendar days after administration of the subject's last dose or exposure to investigational product.

Serious AEs require immediate notification to the Sponsor or its designated representative. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study product is suspected.

12.3. Definition of an Adverse Event

An AE is any untoward medical occurrence that occurs in a subject after they have signed an informed consent for a trial involving an investigational product. Any AE that occurs after the informed consent has been signed, until first usage of investigational product, will be considered non-treatment emergent and cannot (by virtue of time of occurrence) have a causal relationship with the investigational product.

The event does not need to have a suspected causal relationship with the investigational product or device. Therefore, an AE can be any unfavorable and unintended sign, symptom, disease or injury temporally associated with the use of an investigational product whether or not related to the investigational product. Examples of adverse events include but are not limited to:

- Abnormal test findings,
- Clinically important symptoms and signs,

- Changes in physical examination findings,
- Hypersensitivity, and
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Overdose,
- Withdrawal,
- Abuse,
- Drug misuse,
- Drug interactions,
- Medication errors,
- Product dependency,
- Exposure *in utero*, and
- Study related procedure.

12.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a discontinuation from the study, significant additional concomitant treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator or the Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

12.5. Serious Adverse Events (SAE) for Drugs

An AE or suspected adverse reaction is considered “serious” for a drug study if, in the view of either the Investigator (MD/DO/ DMD/DDS) or the Sponsor, it results in any of the following outcomes:

- Results in death,
- Is life-threatening (immediate risk of death),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,

- Results in congenital anomaly/birth defect,
- Is considered medically significant (medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an Emergency Room or at home, blood dyscrasia, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignancy), or,
- Is a suspected transmission of any infectious agent via a medical product (medically significant) and should be reported as an SAE in the category 'Other medically important conditions.'

12.6. Hospitalization

Adverse events reported from clinical studies associated with hospitalization or prolonging hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Hospitalization does not include the following:

- Rehabilitation facilities,
- Hospice facilities,
- Respite care (e.g., caregiver relief),
- Skilled nursing facilities,
- Nursing homes,
- Emergency room visits (unless the reason for the emergency room visit meets one of the other outcomes in the definition of serious), and/or
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:
 - Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
 - Social admission (e.g., subject has no place to sleep),
 - Administrative admission (e.g., for yearly physical exam),
 - Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol),

- Optional admission not associated with a precipitating clinical AE (e.g., or elective cosmetic surgery),

Pre-planned treatments or surgical procedures should be noted in the baseline source documentation for the entire protocol and/or for the individual subject.

- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

12.7. Resolution

The Investigator will be required to assess the outcome of the AE for investigational product as one of the following:

- Resolved,
- Not Resolved,
- Fatal,
- Resolved with sequelae,
- Resolving, or
- Unknown.

Any causally-related AEs unresolved upon completion of the last study visit will be followed up by the study staff until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and recorded in the EDC system. An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the Investigator and has concurrence by the Sponsor.

12.8. Severity Assessment

The severity of AEs from investigational product will be assessed by the Investigator or medically qualified individual (MD/DO/ DMD/DDS) using the following general categorical descriptors:

MILD:	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with subject's usual function or normal everyday activities
MODERATE:	Sufficient discomfort is present to cause interference to some extent with subject's usual function or normal everyday activity
SEVERE:	Extreme distress, causing significant impairment of functioning or incapacitation; interferes significantly with subject's usual function; prevents normal everyday activities

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

12.9. Causality Assessment

- The Investigator's or medically qualified individual (MD/DO/ DMD/DDS) assessment of causality for investigational product (i.e., relationship to investigational product) must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.
- Not Related - An AE that is not related to the use of the drug
- Doubtful - An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship to investigational product is unlikely.
- Possible - An AE that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship to investigational product cannot be excluded.
- Probable - An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge) and an alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- Very Likely - An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge) for a causal relationship to the drug.

If the Investigator determines a SAE is associated with study procedures, the Investigator must record this suspected causal relationship in the source documents and in the EDC system, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

12.9.1. Withdrawal Due to Adverse Events

When a subject withdraws due to a SAE, the SAEs must be reported in accordance with the reporting requirements defined below.

12.9.2. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

12.9.3. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for a SAE. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

For randomized subjects, all AEs will be reported on the AE source document page and then will be entered in EDC. A Clinical Serious Adverse Event (SAE) Report Form must also be completed if the event is considered to be serious. It should be noted that this Clinical SAE Report Form for collection of SAE information is not the same as the AE EDC page. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both

forms. Adverse events should be reported using concise medical terminology in the EDC system as well as on the form for collection of SAE information.

12.9.3.1. Serious Adverse Event Reporting Requirements

If a SAE occurs, the Sponsor is to be initially notified by telephone immediately upon awareness of the event by the Investigator's site. Within 24 hours of the Investigator site's awareness of the event, the study site must send the Sponsor the Clinical SAE Report Form (via a secure e-mail). This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EIU cases. In the rare event that the Investigator's site does not become aware of the occurrence of a SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigator's site is to report the event immediately after learning of it as described and document the time of the study site's first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings (if available) and death certificate should be collected if permission is obtained from the subject's family. For a hospitalization, a copy of the hospital discharge summary should be requested. If obtained, these documents (with subject's personal identifiers redacted) should be submitted as soon as possible to the Sponsor or its designated representative.

Appropriate SAE forms will be provided to the study site at the initiation of the study. Upon notification of an SAE at the study site, the Investigator or designated study site staff should call and speak to their Sponsor's study team contact immediately to initially notify them of the SAE.

Within 24 hours of awareness of the event, the Investigator or designated study site staff:

- Complete the Clinical SAE Report Form [that has been provided to you by the Sponsor or their designee] with as much information as possible, however at a minimum, the subject identification number, name of product, SAE, and name of reporter are required);
- Ensures the Investigator signs the Clinical SAE Report Form **prior to** sending to the Sponsor;
- Scans and send via secure email the Clinical SAE Report Form and any supportive documentation to the Sponsor contacts.
- The Sponsor contact information:

[REDACTED]

12.10. Special Situations

Special Situations (SS): Safety events that may not meet the definition of an AE; however, are required to be collected to meet Health Authority requirements. Examples include:

- Overdose of a J&J medicinal product.
- Pregnancy exposure (maternal and paternal) to a J&J medicinal product or medical device.
- Exposure to a J&J product from breastfeeding.
- Suspected abuse/misuse of a J&J medicinal product or medical device.
- Inadvertent or accidental exposure to a J&J medicinal product or medical device (including occupational exposure).
- Any failure of expected pharmacological or medical device action (i.e., lack of effect) of a J&J product.
- Unexpected therapeutic or clinical benefit from use of a J&J product.
- Medication error involving a J&J medicinal product or medical device with or without patient/consumer exposure to the J&J product, (e.g., product name confusion) OR that caused an unintended effect or could cause an intended effect (e.g. adult medicine given to a young child).
- Suspected transmission of an infectious agent via a J&J product.
- Off-label use. *Note: Off-label use of a product without an associated AE should be collected only when it is specifically and voluntarily brought to the attention of the company in an unsolicited manner by a reporter (e.g., Patient or HCP), or data obtained from databases where off-label use may be systematically collected (e.g., reimbursement database in US), and in accordance with local procedure in compliance with local laws and regulations.*

12.11. Exposure In Utero

For investigational products within clinical studies and for marketed products, an exposure *in utero* EIU occurs if:

1. A woman is exposed to the investigational product at any time between her last menses prior to conception through the delivery of the baby.
2. There is a possibility of intrauterine exposure to drug via semen from the male partner who is taking the investigational product at the time of conception, thereby possibly exposing the fetus to the product.

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's participation, the Investigator must report the pregnancy to the Sponsor on a Pregnancy Notification Form (to be provided by the Sponsor when applicable). In addition, the Investigator must submit information regarding environmental exposure to a Sponsor product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy Notification Form. This must be done irrespective of whether an adverse event has occurred and notification must occur within 24 hours of awareness of the pregnancy. Initial notification via telephone to the Sponsor's study team contact must occur immediately upon the Investigator site's awareness of the pregnancy. The Pregnancy Notification Form must then be sent to the Sponsor within 24 hours of the site's awareness. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports. The Investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The Investigator will provide this information as a follow-up to the initial Drug Exposure During Pregnancy Collection Form A and/or End of Pregnancy Collection Form B (provided by the Sponsor when applicable). The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a SAE case is created with the event of ectopic pregnancy.

The Investigator should follow the procedures for reporting SAEs if the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]). In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an End of Pregnancy Collection Form B can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional pregnancy outcomes that are classified as SAEs and should be reported as such include:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth, without regard to causality.
- Any infant death after 1 month that the Investigator assesses as possibly related to *in utero* exposure to the investigational product.

13. STATISTICS

The Sponsor's [REDACTED] will be responsible for data management and statistical analyses. Detailed methodology for the statistical analysis of the data will be documented in the Statistical Analysis Plan to be finalized and approved prior to database lock and release of randomization.

13.1. Sample Size Determination

This study is to demonstrate the therapeutic equivalence of the new formulation of [REDACTED] to the current formulation based on the change from baseline in redness at 60 seconds after the initial eye drop. To determine the equivalence range, a meta-analysis was conducted. First, a sub-team was established and developed the search criterion and conducted a broad search of historical studies. [REDACTED]

[REDACTED] The estimated overall effect of [REDACTED] versus placebo after 1 minute of eye drop from the meta-analysis was [REDACTED]

13.2. Analysis Sets

13.2.1. Efficacy Analyses Sets

13.2.2. Safety Analysis Set

The safety analysis will be based on all randomized subjects who use at least one dose of investigational product.

13.2.3. Baseline and Demographics

Descriptive statistics (number of subjects, mean, and standard deviation, median, minimum and maximum value for continuous variables; the number and percentage of subjects in each response

category for categorical variables) will be provided for demographic and baseline characteristics for all randomized subjects by treatment sequence.

13.3. Efficacy Analysis

13.3.1. Primary Endpoint

The change from baseline in redness at 60 seconds after the initial eye drop will be analyzed using the

[REDACTED]

13.3.2. Secondary Endpoint

The assessment of redness at other time points will be analyzed in the same way as for the analysis of the primary endpoint.

[REDACTED]

13.4. Statistical Hypothesis

The objective of this study is to demonstrate the equivalence of the test formulation to the control formulation. The statistical hypothesis is stated as

[REDACTED]

13.5. Data Computations and Data Imputations

13.5.1. Data Computations

[REDACTED]

13.5.2. Data Imputations

[REDACTED]

13.6. Analysis Method

13.6.1. Primary Endpoint

The analysis of primary endpoint is described in section 13.3.1.

13.6.2. Secondary Endpoint

The analyses of secondary endpoints are described in section 13.3.2.

13.6.3. Safety Analysis

The safety analysis will be based on the safety analysis set.

13.6.3.1. Adverse Events

The number and percentage of subjects experiencing treatment emergent AEs and treatment-related AEs will be tabulated by treatment using the MedDRA coding dictionary. Subjects experiencing SAEs will be listed. Treatment-related AEs will include events marked as being at least possibly related to study treatment. Subjects will be counted only once for each system organ class and preferred term.

13.6.3.2. Interim Analysis

Not applicable.

13.6.3.3. Data Monitoring Committee

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection(s) by providing direct access to source data/documents.

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Johnson & Johnson will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities the site's responsibility with regard to protocol adherence as well as the study and monitoring responsibilities of Johnson & Johnson or its representatives. These responsibilities will be documented in a Clinical Study Agreement between Johnson & Johnson and the investigator.

During the study, a monitor from Johnson & Johnson or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the source documents and case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report all protocol deviations not previously sent to Johnson & Johnson.
- Confirm AEs and SAEs have been properly documented in the EDC system and confirm any SAEs have been forwarded to Johnson & Johnson and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or study-related direction.

14.2. Audits and Inspections

Authorized representatives of Johnson & Johnson, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Johnson & Johnson audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact their study contacts immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained in the Site Master File by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Johnson & Johnson may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Forms / Electronic Data Capture

As used in this protocol, the term case report form (CRF) should be understood to refer to the Electronic Data Capture system.

All data will be collected on source documents first and then recorded in the Electronic Data Capture (EDC) system.

The EDC system, is the database where pertinent study data is collected such as demography, subject randomization, ocular assessments, adverse events, and subject disposition.

Electronic Data Capture pages should be completed for each randomized subject. The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

It is the Investigator's responsibility to ensure completion and to review and approve all information captured in the EDC. The subject's data in the EDC system must be electronically signed by the Investigator. These signatures serve to attest that the information contained in the EDC system is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical data entered in the EDC. Subject source documents are the Investigator's subject records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts.

All final data recorded in EDC system will be kept by the Sponsor and at the clinical site.

All data recorded on source documents will be kept at the clinical site.

16.2. Inspection of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

16.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Johnson & Johnson or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

If the investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

17. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the sponsor. In addition, the sponsor retains the right to discontinue development of this investigational compound at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the investigator must contact all participating subjects within 2 weeks. All study materials must be collected and all CRFs completed to the greatest extent possible.

18. DEFINITION OF END OF STUDY

The end of this study will be when the last subject completes their last visit.

19. PUBLICATION POLICY

Publication of study results by the Investigator is discussed in the Clinical Study Agreement, as appropriate. Results from this study may be published in the form of oral or written presentations at scientific meetings or as one or more peer-reviewed journal articles. In these cases, no information on individual subjects will be revealed.

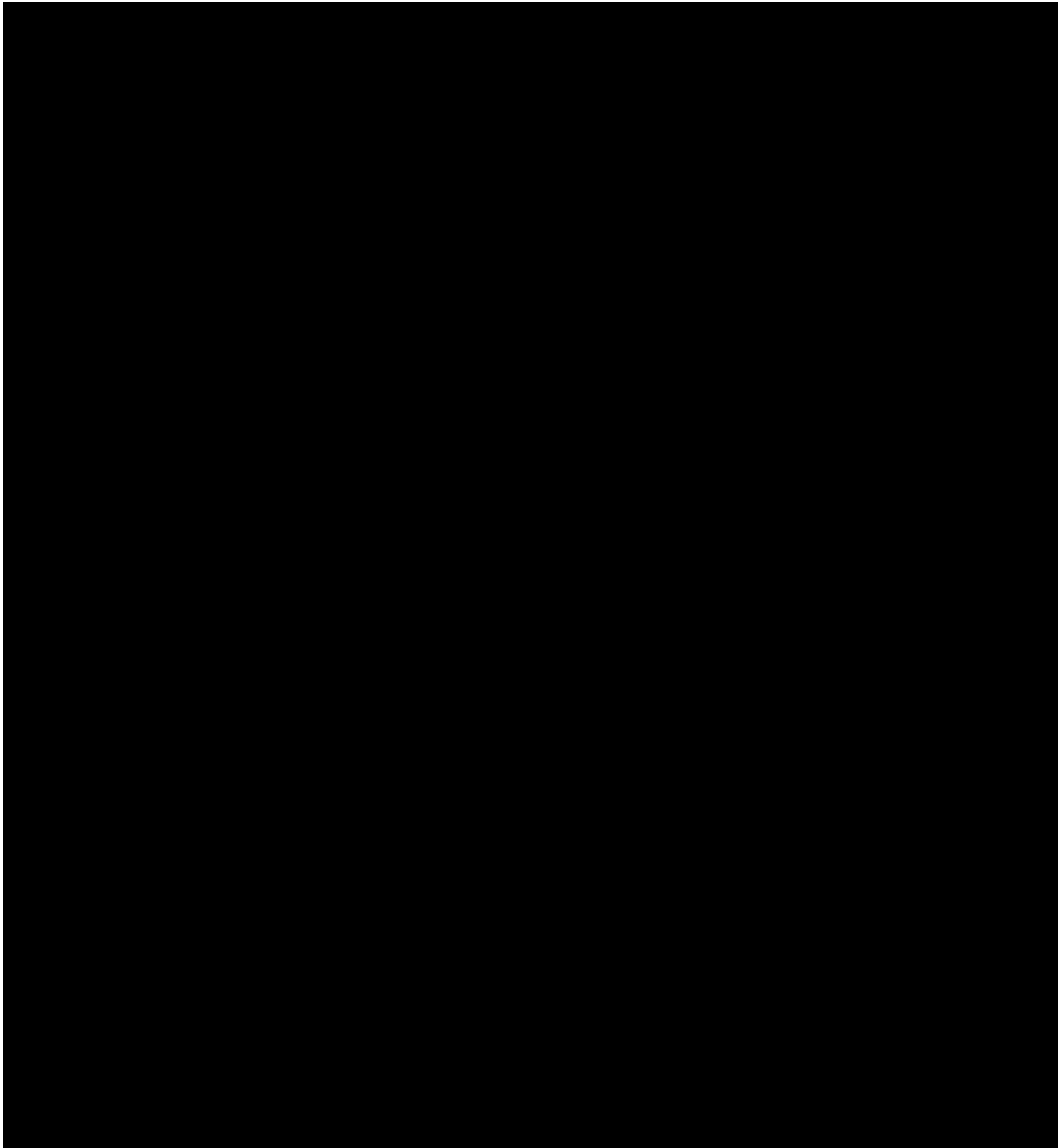
20. LIST OF REFERENCES

1. Cronau, H.; Kankanala, R.R.; Mauger, T. *Diagnosis and Management of Red Eye in Primary Care. American Family Physician.* 2010;81(2):137-144, 145.
2. Hara, J.H.. *The red eye: diagnosis and treatment.* American Family Physician. 1996 Dec; 54(8): 2423-30.
3. Murphy, P.J.; Lau, J.S.S; Sim, M.M.L; Woods, R.L. *How red is a white eye? Clinical grading of normal conjunctiva hyperaemia.* Eye. 2007 (21): 633-638.
4. [REDACTED]

21. APPENDIX 1 - PROCEDURES, TESTS, EQUIPMENT AND TECHNIQUES

Visual Acuity Procedures





Slit Lamp Biomicroscopy



22. APPENDIX 2 – SUBJECT QUESTIONNAIRES

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