Johnson & Johnson Vision Care, Inc.

Clinical Study Protocol

Clinical Evaluation of an Investigational Lipid Drop in Non-contact Lens Wearing Patients

Protocol Number CR-6328

Version: 4.0

Date: 13 August 2019

Investigational Products: Investigational lipid eye drops and blink® Tears Eye Drops

Key Words: artificial tears, dispensing, Visual Analogue Scale (VAS) comfort, dry eye, subject-reported ocular symptoms (SROS)

Statement of Compliance to protocol, GCP and applicable regulatory guidelines:
This trial will be conducted in compliance with the protocol, ISO 14155[1] the International Conference for Harmonization Good Clinical Practice E6 (ICH-GCP)[2], the Declaration of Helsinki[3], and all applicable regulatory requirements.

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

PROTOCOL TITLE, NUMBER, VERSION

Title: Clinical Evaluation of an Investigational Lipid Drop in Non-contact Lens Wearing Patients
Protocol Number: CR-6328
Version: 4.0
Date: 13 August 2019

SPONSOR NAME AND ADDRESS

Johnson & Johnson Vision Care, Inc. (JJV)
7500 Centurion Parkway
Jacksonville, FL 32256

MEDICAL MONITOR

[redacted]

The Medical Monitor must be notified by the clinical institution/site by e-mail, fax, or telephone within 24 hours of learning of a Serious Adverse Event. The Medical Monitor may be contacted during business hours for adverse event questions. General study related questions should be directed towards your assigned clinical research associate.

The Medical Monitoring Plan is maintained as a separate document and included in the Trial Master File.

AUTHORIZED SIGNATURES

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations,[4] ICH guidelines,[2] ISO 14155,[1] and the Declaration of Helsinki.[3]

Author/Study Responsible Clinician	**See Electronic Signature Report**	DATE
Clinical Operations Manager	**See Electronic Signature Report**	DATE
Biostatistician	**See Electronic Signature Report**	DATE
Data Management	**See Electronic Signature Report**	DATE
Fellow Reviewer	**See Electronic Signature Report**	DATE
Approver	**See Electronic Signature Report**	DATE
Approver	**See Electronic Signature Report**	DATE

CHANGE HISTORY

Version	Originator	Description of Change(s) and Section Number(s) Affected	Date
1.0	[redacted]	Original Protocol	23 May 2019
2.0	[redacted]	Updated PRO Specifications and reordered steps in Unscheduled Visit	30 May 2019
3.0	[redacted]	Correction to dispensing period duration; increase enrollment limit to 150 subjects	29 July 2019
4.0	[redacted]	Correction to study visit window	13 August 2019

SYNOPSIS

Protocol Title	Clinical Evaluation of an Investigational Lipid Drop in Non-contact Lens Wearing Patients
Sponsor	JJV, 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Confirmatory, Phase 1
Trial Registration	This study will be registered on ClinicalTrials.gov based on the following: this confirmatory study meets the criteria for registration in [redacted]
Test Article(s)	Two artificial tears products: • Investigational lipid eye drops – 9618X (Test) • Blink® Tears eye drops (Control)
Treatment dosage	Dosage: Instill 1-2 drops OU 3-4 times a day.
Objectives	The objective of this study is to evaluate the safety and the efficacy of the Investigational lipid eye drops (Test) by comparison with blink® Tears eye drops (Control). This study is being conducted to support product registration in the Europe Union.
Study Endpoints	Primary endpoint(s): • Change in overall ocular comfort from baseline at 30-Day follow-up using VAS Secondary endpoint(s): • Corneal staining Grade 2 or higher using FDA scale • Change in overall quality of vision from baseline at 7-Day and 30-Day follow-up collected using VAS • Subject's reported ocular symptoms (yes/no) • Change in overall ocular comfort from baseline at 7-Day follow-up collected using VAS Other Endpoint(s) • Tear film break up time • Slit Lamp Findings using FDA scale • End of day ocular comfort • Snellen best corrected distance visual acuity • Subjective Evaluation of Symptom of Dryness • Adverse Events • Number and reasons for discontinuation will be monitored.
Study Design	This is a 30-Day, multi-site, double masked, bilateral, active-controlled, 2-Arm parallel group study. Subjects are scheduled for 3 study visits (screening/baseline, 7-Day and 30-Day follow-up visits) over a period of one month.
Sample Size	Approximately 150 subjects (60 per arm) will be enrolled and approximately 112 subjects (56 per arm) are targeted to complete the study.
Study Duration	The study will last approximately 2 months and include a 1-month enrollment period.

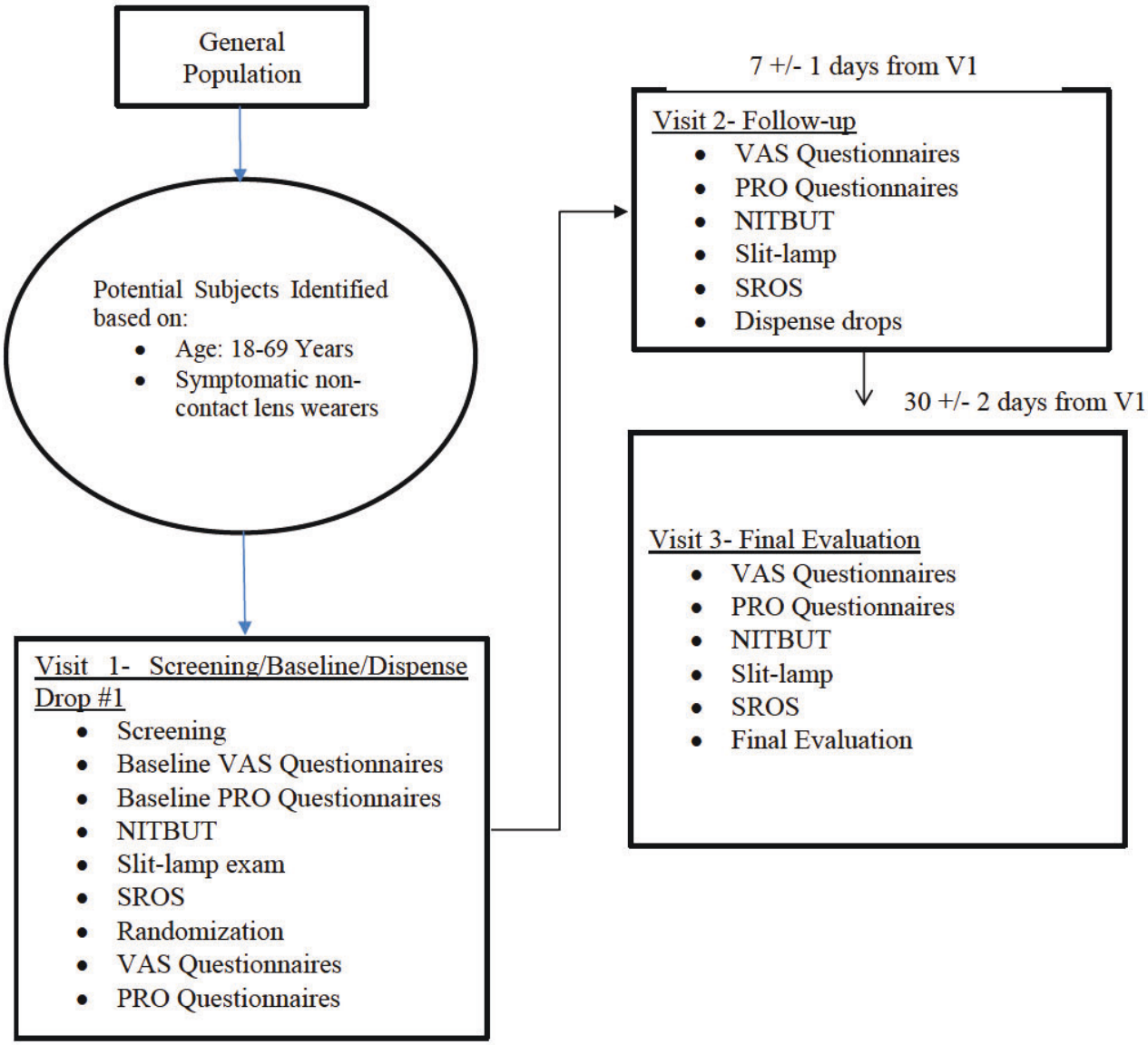
Anticipated Study Population	Non-contact lens wearers 18-69 years of age with self-reported symptoms of ocular dryness or irritation and/or the use of artificial tears in the last 3 months.

Eligibility Criteria	Potential subjects must satisfy all the following criteria to be enrolled in the study: 1. Subjects must be at least 18 years of age and no more than 69 years of age (inclusive). 2. Subjects must be non-contact lens wearers. 3. Subjects must achieve visual acuity of 20/30 or better in each eye, either unaided or best corrected. 4. Subjects must possess a functional/usable pair of spectacles and bring them to the visit (only if applicable - to the investigator's discretion). 5. Self-reported symptoms of ocular dryness or irritation and/or the use of artificial tears in the last 3 months. 6. Subjects must read, understand, and sign the Statement of Informed Consent 7. Subjects must appear able and willing to adhere to the instructions set forth in this clinical protocol. Potential subjects who meet any of the following criteria **will be excluded** from participating in the study: 1. Currently pregnant or breast-feeding. 2. Diabetes. 3. Any ocular or systemic allergies or disease which may interfere with the clinical trial (at the discretion of the investigator). 4. Any systemic disease, autoimmune disease, or use of medication which may interfere with the clinical trial (at the discretion of the investigator). 5. Any infectious diseases (e.g. hepatitis, tuberculosis) or a contagious immunosuppressive disease (e.g. HIV), by self-report. 6. Any Grade 3 or greater biomicroscopy findings (this includes, corneal edema, corneal staining, corneal vascularization, conjunctival injection, tarsal abnormalities, bulbar injection) on the FDA classification scale. 7. Any active ocular abnormalities/conditions that may interfere with the clinical trial (this includes, but not limited to, chalazia, recurrent styles, pterygium, infection, etc.). 8. Any corneal distortion due to previous rigid gas permeable lens wear, surgery or pathology. 9. History of any ocular or corneal surgery (e.g. RK, PRK, LASIK) 10. Participation in any pharmaceutical or medical device related clinical trial within 30 days prior to study enrollment.

	11. History of binocular vision abnormality or strabismus. 12. Habitual wearers of soft contact lenses within the past 1 month or rigid gas permeable lens within the past 3 months 13. Current habitual use of Prescription Medication to treat dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator) 14. Employees of investigational clinic (investigator, coordinator, and technician etc) or family members of an employee of the clinical site by self-report. In addition to the above criteria, patients with any allergy or sensitivity to ingredients that this product may contain (Castor Oil, Polyoxyl 40 Hydrogenated Castor Oil, Sodium Chlorite, Boric Acid, Sodium Borate Decahydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Polyethylene Glycol 400, Sodium Hyaluronate, Purified Water) should not participate in the study.

Disallowed Medications/Interventions	Current habitual use of Prescription Medicines to treat dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).
Measurements and Procedures	Subjective assessment of ocular comfort using visual analog scale (VAS), subjective evaluation of symptom of dryness, Snellen visual acuity, slit lamp finding using FDA scale, tear film break time, subjective reported ocular symptoms.
Microbiology or Other Laboratory Testing	None
Study Termination	The occurrence of one or more Unanticipated Adverse Device Effect (UADE), or any SAE where relationship to study agent cannot be ruled out, will result in stopping further dispensing investigational product. In the event of a UADE or SAE, the Sponsor Medical Monitor may unmask the treatment regimen of subject(s) and may discuss this with the Principal Investigator before any further subjects are enrolled.
Ancillary Supplies/ Study-Specific Materials	ScleralFil (Bausch + Lomb), LacriPure (Menicon), Fluorescein (Akorn, Inc.) or other country-specific alternative approved by the sponsor.
Principal Investigator(s) and Study Institution(s)/Site(s)	A full list of Principal Investigators, clinical sites, and institutions is kept separately from the Study Protocol and is included in the study Trial Master File.

Figure 1: Study Flowchart



COMMONLY USED ABBREVIATIONS AND DEFINITIONS OF TERMS

ADD	Plus Power Required For Near Use
ADE	Adverse Device Effect
AE	Adverse Event/Adverse Experience
BCVA	Best Corrected Visual Acuity
BSCVA	Best Spectacle Corrected Visual Acuity
CE	Conformité Européene
CEH	Consumer Eye Health
CFR	Code of Federal Regulations
COAS	Complete Ophthalmic Analysis System
COM	Clinical Operations Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Center Thickness
[redacted]	[redacted]
D	Diopter
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
JJV	Johnson & Johnson Vision, Inc.
LC	Limbus Center
LogMAR	Logarithm of Minimal Angle of Resolution
MedDRA©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIH	National Institutes of Health
OD	Right Eye
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
OS	Left Eye
OSDI	Ocular Surface Disease Index
OU	Both Eyes
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIG	Patient Instruction Guide
PQC	Product Quality Complaint
PRO	Patient Reported Outcome

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VA	Visual Acuity

1. INTRODUCTION AND BACKGROUND

It is estimated that over 16 million US adults have been diagnosed with dry eye.[5] Artificial tears are often used to treat symptoms of ocular dryness and discomfort. Most of the major artificial tear companies have some type of lipid product to address lipid deficient tear films, however JJV CEH does not currently have a lipid-like drop in our portfolio.

This study will be conducted at up to 7 clinical sites in the United States and will include one investigational lipid eye drop (9618X) and one marketed (CE marked) artificial tears (blink® Tears). By developing a lipid-like drop addition to the CEH portfolio it would continue to live into the JJV Eye Health Mission.

1.1. Name and Descriptions of Investigational Products

The products used in this clinical study are listed below:

- Investigational lipid eye drops 9618X (Test)
- Blink® tears eye drops (Control)

1.2. Intended Use of Investigational Products

One of the products is an investigational, preserved lipid drop, and the other product is an FDA and CE approved and marketed eye drop, available over the counter (without a prescription). They will be used as indicated on-label to reduce symptoms of ocular dryness. Subjects will be required to use the 1-2 drops in both eyes 3-4 times a day.

The intended use of the study artificial tears is treatment of subjects with symptoms of ocular dryness.

1.3. Summary of Findings from Nonclinical Studies

See the Investigator's Brochure.

1.4. Summary of Known Risks and Benefits to Human Subjects

The following risks/adverse events can be associated with using artificial tears, in general:

- There may be less comfort than when the drop was first placed on the eye.
- The eyes may burn, sting and/or itch.
- There may be a feeling of something in the eye (foreign body, scratched area).
- There may be the potential for some temporary impairment due to peripheral infiltrates, peripheral corneal ulcers and corneal erosion.

- There may be the potential for other physiological observations, such as local or generalized edema, corneal neovascularization, corneal staining, injection, tarsal abnormalities, iritis and conjunctivitis, some of which are clinically acceptable in low amounts.
- There may be excessive watering, unusual eye secretions, or redness of the eye.
- Poor visual acuity, blurred vision, rainbows or halos around objects, photo-phobia, or dry eyes may also occur if the drops are used continuously or for too long a time.

There is no direct benefit to the subject for participating in the study, although they will be able to try out new artificial tears. The information from this study will aid if the further development and design of new artificial tears.

For the most comprehensive clinical information regarding the artificial tears refer to the package inserts [redacted]

1.5. Relevant Literature References and Prior Clinical Data Relevant to Proposed Clinical Study

Refer to the Investigator's Brochure and package insert [redacted] for additional information.

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Objectives

The objective of this study is to evaluate the safety and efficacy of the investigational lipid eye drops (Test) by comparison with blink® Tears eye drops (Control).

This study is being conducted with the primary intent to support registrations in Europe.

2.2. Endpoints

Primary Endpoint:

The primary endpoint in this study is change in overall ocular comfort score from baseline at 30-Day follow-up. Subjective overall ocular comfort will be assessed at baseline, 7-Day and 30-Day follow-up using a Visual Analogue Scale (VAS)[6,7] with continuous scale from 0 (extremely uncomfortable) to 100 (extremely comfortable).

Secondary endpoints:

- Corneal staining Grade 2 or higher using FDA scale
- Change in overall quality of vision from baseline at 7-Day and 30-Day follow-up using VAS
- Subject's reported ocular symptoms (yes/no)
- Change in overall ocular comfort from baseline at 7-Day follow-up using VAS

Other Endpoints:

- Tear film break up time
- Slit lamp findings using FDA scale
- End of day ocular comfort
- Snellen best corrected distance visual acuity

- Subjective evaluation of symptom of dryness
- Adverse Events
- Number and reasons for discontinuation will be monitored.

2.3. Hypotheses

Primary hypotheses:

1. The Test eye drops will be non-inferior to the Control eye drops with respect to change in ocular comfort from baseline at 30-Day follow-up. A non-inferiority margin of -20 point ocular comfort VAS scale will be used.

Secondary hypotheses:

1. The proportion of eyes with Grade 2 or higher corneal staining in the Test group will be no different to that in the Control group.

2. The change in overall quality of vision from baseline at 7-Day and 30-Day follow-up of the Test eye drops will be no different to that of the Control eye drops.

3. The proportion of eyes with reported ocular symptoms in the Test group will be no different to that in the Control group.

4. The Test eye drops will be non-inferior to the Control eye drops with respect to change in ocular comfort from baseline at 7-Day follow-up. A non-inferiority margin of -20 point ocular comfort VAS scale will be used.

3. TARGETED STUDY POPULATION

3.1. General Characteristics

The study populations will be healthy non-contact lens wearers between 18-69 years of age from up to 7 sites in the US.

3.2. Inclusion Criteria

Potential subjects must satisfy all the following criteria to be enrolled in the study:

1. Subjects must be at least 18 years of age and no more than 69 years of age (inclusive).
2. Subjects must be non-contact lens wearers.
3. Subjects must achieve visual acuity of 20/30 or better in each eye, either unaided or best corrected.
4. Subjects must possess a functional/usable pair of spectacles and bring them to every visit (only if applicable - to the investigators discretion).
5. Self-reported symptoms of ocular dryness or irritation and/or the use of artificial tears in the last 3 months.
6. Subjects must read, understand, and sign the Statement of Informed Consent.
7. Subjects must appear able and willing to adhere to the instructions set forth in this clinical protocol.

3.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Currently pregnant or breast-feeding.
2. Diabetes.
3. Any ocular or systemic allergies or disease which may interfere with the clinical trial (at the investigator's discretion).
4. Any systemic disease, autoimmune disease, or use of medication which may interfere with the clinical trial (at the investigator's discretion).
5. Any infectious diseases (e.g. hepatitis, tuberculosis) or a contagious immunosuppressive disease (e.g. HIV), by self-report.
6. Any Grade 3 or greater biomicroscopy findings (this includes, corneal edema, corneal staining, corneal vascularization, conjunctival injection, tarsal abnormalities, bulbar injection) on the FDA scale.
7. Any active ocular abnormalities/conditions that may interfere with the clinical trial (this includes, but not limited to, chalazia, recurrent styles, pterygium, infection, etc.).
8. Any corneal distortion due to previous rigid gas permeable lens wear, surgery or pathology.
9. History of any ocular or corneal surgery (e.g. RK, PRK, LASIK).
10. Participation in any pharmaceutical or medical device related clinical trial within 30 days prior to study enrollment.
11. History of binocular vision abnormality or strabismus.
12. Habitual wearers of soft contact lenses in the past 1 month or rigid gas permeable lens within the past 3 months.
13. Current habitual use of Prescription Medicines to treat dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).
14. Employees of investigational clinic (investigator, coordinator, and technician, etc.) or family member of an employee of the clinical site by self-report.

In addition to the above criteria, patients with any allergy or sensitivity to ingredients that this product may contain (Castor Oil, Polyoxyl 40 Hydrogenated Castor Oil, Sodium Chlorite, Boric Acid, Sodium Borate Decahydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Polyethylene Glycol 400, Sodium Hyaluronate, Purified Water) should not participate in the study.

3.4. Enrollment Strategy

Study subjects will be recruited from the clinical site's subject database and/or utilizing Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved materials.

4. STUDY DESIGN AND RATIONALE

4.1. Description of Study Design

This is a 30-Day multi-site, randomized, double masked, bilateral, controlled, 2-Arm parallel group study. Approximately 150 subjects will be screened and randomly assigned to either Test or Control group (60 subjects/arm). The goal is for a sample size of 112 after subjects who withdraw or are lost-to-follow-up. Subjects are scheduled for 3 study visits (screening/baseline, 7-Day and 30-Day follow-up visits) over a period of one month.

At Visit 1, subjects will be consented and screened for inclusion/exclusion criteria. If a subject is found to meet all eligibility criteria, they will be dispensed with artificial tears eye drops based on the randomization scheme; otherwise, the subject will be discontinued from the study. Subjects will be dispensed with their randomly assigned eye drops and instructed to use them in both eyes, 3-4 times a day over a 7±1 day period. The follow-up evaluation (Visit 2) will occur 7±1 days after Visit 1.

At Visit 2, VAS and PRO questionnaires, SROS and slit lamp findings will be evaluated, and the subject will be dispensed with a new bottle of drops. Subjects will be instructed to use them in both eyes 3-4 times a day until the next scheduled study visit. Visit 3 will take place 30+/-2 days after Visit 1.

At Visit 3, VAS and PRO questionnaires, SROS, NITBUT and slit lamp findings will be evaluated, and the subject will have a final evaluation before exiting from the study.

4.2. Study Design Rationale

Randomized, double masked, controlled designs are the gold standard to perform scientifically sound evaluations of the intervention by reducing bias associated with the conduct and interpretation of a clinical trial and avoiding confounding from other factors. A 30 Day period is recommended for follow up in pivotal studies[8], and is an appropriate review period based on studies which recognize the impact of cyclical changes to tear quality in female subjects.[9]

4.3. Enrollment Target and Study Duration

A total of up to 150 subjects will be enrolled (informed consent signed) and randomized (60 per arm) from up to 7 clinical sites in the US. The goal is for a sample size of 112 subjects (56 per arm) after subjects who withdraw or are lost to follow-up.

The Investigator is responsible for ensuring that all subjects entering the study conform to subject selection criteria. The number of subjects targeted for randomization and completion are as follows:

Table 1: Target number of subjects by arm and site

	Test	Control	Total
Randomization	60	60	120
Completion	56	56	112
Number of sites	7	7	7
Number of subjects/site Min-Max	8-13	8-13	16-26

The study will last approximately 2 months and include a 1-month enrollment period.

Once the informed consent has been signed the subject will be considered enrolled.

An additional subject may be enrolled if a subject discontinues from the study prematurely.

5. TEST ARTICLE ALLOCATION AND MASKING

5.1. Test Article Allocation

Subjects will be randomly assigned to either Test or Control group based on a computer-generated randomization schedule prepared before the start of the study. The randomization will be stratified by investigational site and randomly permuted blocks of 4 assignments will be used within each study site. The randomization scheme will be generated using the PROC PLAN procedure from the Statistical Analysis System (SAS) Software version 9.4 or higher [10]

The study site will follow the randomization scheme provided and will complete enrollment according to the randomization list and will not pre-select or assign subjects. The assignment of the subjects must be performed at the first baseline visit (Visit 1). The following must have occurred prior to randomization:

- Informed consent has been obtained
- Subject meets all the inclusion / exclusion criteria
- Subject history and baseline information has been collected

5.2. Masking

This is a double-masked study where subjects and the investigators are masked to the identity of the eye drops during the study period. Every attempt will be made to keep the other clinical trial personnel involved in the study (e.g., Data management, Biostatistician) unaware of the identity of the test articles.

The identity of the investigational products will be masked by over labeling the eye drop bottles with a label containing the study number, expiration date and the randomization codes. Only the personnel involved in the over labeling and the unmasked Statistician generating the randomization scheme will have access to the decode information translating the randomization codes into Test and Control eye drops. The medical monitor will also have access to the decode information in case breaking the mask is necessary for the urgent medical treatment of a subject.

5.3. Procedures for Maintaining and Breaking the Masking

Under normal circumstances, the mask should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the Investigator may, in an emergency, contact the medical monitor. In the event the mask is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unmasking must be documented in the

subject record. The Investigator is also advised not to reveal the study treatment assignment to the clinical site or Sponsor personnel.

When dispensing test articles, the following steps should be followed to maintain randomization codes:

1. Investigator or designee (documented on the Delegation Log) will consult the randomization scheme to obtain the test article assignment for that subject prior to dispensing
2. Investigator or designee will record the subject's number on the appropriate line of the randomization scheme
3. Investigator or designee will pull the appropriate test articles from the study supply. All test articles that are opened, whether dispensed (placed/fit on eye or dispensed outside the clinical site) or not, must be recorded on the Test Article Accountability Log in the "Dispensed" section

6. STUDY INTERVENTION

6.1. Identity of Test Articles

Table 2: Artificial Tears

	Test	Control
Solution Name/Description	Investigational lipid eye drops (9618X)	Blink® Tears
Manufacturer	Johnson & Johnson Vision, Inc	Johnson & Johnson Vision, Inc
Ingredients	Castor Oil, Polyoxyl 40 Hydrogenated Castor Oil, Sodium Chlorite, Boric Acid, Sodium Borate Decahydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Polyethylene Glycol 400, Sodium Hyaluronate, Purified Water	Sodium Chlorite Boric Acid Sodium Borate Decahydrate Sodium Chloride Potassium Chloride Calcium Chloride Dihydrate Magnesium Chloride Hexahydrate Polyethylene Glycol 400 Sodium Hyaluronate Purified Water
Packaging Form	Over-Labeled	Over-Labeled

6.2. Ancillary Supplies/Products

ScleralFil (Bausch + Lomb), LacriPure (Menicon) and Fluorescein (Akorn, Inc.), or other country-specific alternative approved by the sponsor.

Table 2: Ancillary Supplies

	Solution		
Solution Name/Description	*ScleralFil (or other sponsor-approved product)*	*Lacripure (or other sponsor-approved product)*	*Fluorescein (or other sponsor-approved product)*
Manufacturer	*Bausch + Lomb*	*Menicon*	*Akorn, Inc*
Preservative	*None*	*None*	*None*
Other distinguishing items (dye, packaging, approval status, etc.)	*NA*	*NA*	*D&C Yellow No. 8, 0.6 mg*

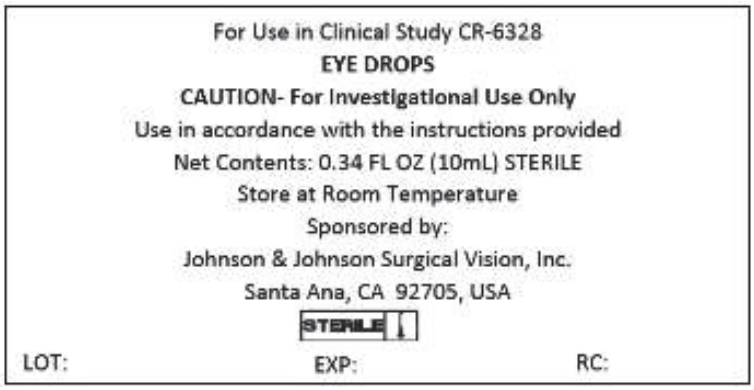
Sodium fluorescein dye will be used for biomicroscopy, as needed. Sterile, preservative-free, saline may be used in this clinical study to rinse each eye.

6.3. Administration of Test Articles

Test articles will be dispensed to subject meeting all eligibility requirements, including any dispensing requirements set forth in this clinical protocol. Subjects will be dispensed an adequate supply of test articles to complete the study. Lost or damaged test articles will not be replaced at the discretion of the Investigator and/or the Sponsor.

6.4. Packaging and Labeling

The test articles will be packaged in bottles as the primary packaging. The test article will be over-labeled to mask the subject to the identity. The test articles will be in investigational cartons sealed with a tamper evident seal, commercial cartons, or in plastic bags as the secondary packaging form. The labels for the primary and secondary packages will contain the following message, in accordance with JJV over-labeling procedures for masked studies involving marketed products: "For Use in Clinical Study CR-6328 Only, Not for Resale. Product Conforms to with CE Mark Requirements." The labels will also contain the product code, lot number, expiration date and the clinical study number.



6.5. Storage Conditions

Test articles will be maintained at ambient temperatures at the clinical site. Test articles must be kept under secure conditions.

6.6. Collection and Storage of Samples

When possible, any test article associated with an Adverse Events and/or a Product Quality Complaint must be retained pending directions from the sponsor for potential return back to JJV.

6.7. Accountability of Test Articles

JJV will provide the Investigator with sufficient quantities of study articles and supplies to complete the investigation. The Investigator is asked to retain all shipment documentation for the test article accountability records.

Test article must be kept in a locked storage room, accessible only to those assigned by the Investigator for dispensing. The Investigator may delegate this activity to authorized study site personnel listed on the Site Delegation Log. All test articles must be accounted. This includes:

1. What was dispensed for the subject
2. What was returned to the Investigator unused
3. The number and reason for unplanned replacements

The Investigator will collect all unused test articles from the subjects at the end of the subject's participation. Subject returned unused test articles must be separated from the clinical study inventory of un-dispensed test articles and must be labeled with the subject number and date of return. Following final reconciliation of test articles by the monitor, the Investigator or monitor will return all unused test articles to JJV.

If there is a discrepancy between the shipment documents and the contents, contact the study monitor immediately.

[redacted]

7. STUDY EVALUATIONS

7.1. Time and Event Schedule

Table 3: Time and Events

Visit Information	**Visit 1 Baseline, dispense drop**	**Visit 2 Follow-up #1**	**Visit 3 Follow-up #2**
Time Point	**Day 0**	**7+/-1 days after V1**	**30+/-2 days after V1**
Estimated Visit Duration	**2.5 hours**	**1 hours**	**1 hours**
Study Informed Consent	X		
Inclusion/Exclusion Screening Criteria	X		
Demographics	X		
Medical History & medication review	X	X	X
Habitual Artificial Tear usage	X		
Biomicroscopy	X	X	X
Eligibility	X		
Randomization	X		
VAS questionnaire	X	X	X
PRO Questionnaire	X	X	X
Non-invasive tear break up time	X	X	X
Drop instillation	X		
Ocular Symptoms	X	X	X
Drop Dispensing & Instruction	X	X	
Drop Usage questions	X	X	X
Exit Slit-lamp		X	X
Adverse Event Review		X	X
Final Evaluation			X

7.2. Detailed Study Procedures

VISIT 1

Aim for Visit 1 to occur in the afternoon (after 12 PM). The subjects must present to Visit 1 wearing their spectacles (if applicable). Subjects will be asked to bring their habitual artificial tears with them to the visit (if applicable).

Visit 1: Screening			
Step	Procedure	Details	[redacted]
1.1	Statement of Informed Consent	Each subject must read, understand, and sign the Statement of Informed Consent and Privacy Statement before being enrolled into the study. The Principal Investigator or their designee conducting the informed consent discussion must also sign the consent form. **Note**: The subject must be provided a signed copy of this document.	
1.2	Demographics	Record the subject's date of birth, gender, race and ethnicity.	
1.3	Medical History and Concomitant Medications	Questions regarding the subjects' medical history and concomitant medications.	
1.4	Artificial Tear Use	The subject will be asked about their artificial tear use.	
1.5	Eligibility after Screening	All responses to Screening Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria must be answered "no" for the subject to be considered eligible.	

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
1.6	Entrance Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]
1.7	Baseline SROS	Subjects will respond to a verbal open-ended symptoms questionnaire.	[redacted]
1.8	Baseline VAS	The subject will respond to the VAS questionnaire	
1.9	Baseline PRO questionnaires	The subject will complete the electronic questionnaires using the Kiosk portal.	[redacted]
1.10	Tear break-up time	Record the tear film stability (NITBUT), OD and OS, with a Medmont or other topographer.	[redacted]

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
1.11	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings and determine eligibility. If there are any Grade 3 or higher other slit-lamp findings, the subject is ineligible to continue at this time, but may return up to one additional time to determine eligibility. If discontinued a final examination must be completed. If there are no slit lamp findings, and the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	[redacted]
1.12	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (FDA grading scale) will be assessed using a more detailed scale for internal purposes only.	[redacted]
1.13	Eligibility after Baseline	All responses to Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria questions must be answered "no" for the subject to be considered eligible.	

Visit 1: Dispensing			
Step	Procedure	Details	[redacted]
1.14	Wash out	Allow a washout of at least 5 minutes from the end of the slit-lamp exam before instilling the artificial tear	
1.15	Randomization	Subjects will be randomized to an artificial tear drop (Test or Control).	
1.16	Drop instillation	The subject will instill 1 drop in both eyes (or drops can be instilled by the investigator should the subject require drop installation training). The investigator should observe the subject's technique for drop instillation and recommend new techniques to improve subject safety, if necessary.	
1.17	Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	[redacted]
1.18	Drop Settling	Allow the drop to settle for 5 minutes.	
1.19	VAS Questionnaire	The subject will respond to the VAS questionnaire	[redacted]

Visit 1: Dispensing			
Step	Procedure	Details	[redacted]
1.20	PRO Questionnaire	The subject will complete the electronic questionnaires using the Kiosk portal.	[redacted]
1.21	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]
1.22	Continuance	For the subject to continue in the study, they must meet both of the following criteria: • Visual acuity is 20/30 or better OD and OS • Subject willing to use the drop 3-4 times a day OU for 7 +/- 1 days.	
1.23	Instillation of drops training, if necessary	Instruct and teach instillation of drops.	
1.24	Dispense	The artificial tears will be dispensed for a 7 +/- 1 day dispensing period • Dispense enough artificial tears to last the whole week. • A patient instruction guide will be provided and the subject will be instructed not to use other artificial tears during the dispensing period. • Subjects will be scheduled for Visit 2 in approximately 7 +/- 1 days.	

VISIT 2

Aim for Visit 2 to occur in the afternoon (after 12 PM). The subjects must present to visit 2 wearing their habitual spectacles (if applicable) having used the study drop in both eyes at least 2 times that day.

Visit 2: 7-day Follow-up			
Step	Procedure	Details	[redacted]
2.1.	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
2.2.	Artificial Tear Compliance	Confirm the subject used the drops as instructed.	
2.3.	Collect bottle	The bottle will be collected by the site staff and discarded.	
2.4.	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	[redacted]
2.5.	VAS Questionnaire	The subject will respond to the VAS questionnaire	[redacted]

Visit 2: 7-day Follow-up			
Step	Procedure	Details	[redacted]
2.6.	PRO Questionnaire	The subject will complete the electronic questionnaires using the Kiosk portal.	[redacted]
2.7.	Preference Question	The subject will complete the electronic preference questions using the Kiosk portal, if applicable.	[redacted]
2.8.	Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]
2.9.	Tear Break up time	Record the tear film stability (NITBUT), OD and OS, with a Medmont or other topographer.	[redacted]
2.10.	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings. (All ocular AE's must be followed to resolution) If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	[redacted]
2.11.	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (1.0 scale units) will be assessed using a more detailed scale for internal purposes only.	[redacted]
2.12.	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]
2.13.	Continuance	For the subject to continue in the study, they must meet both of the following criteria: • Visual acuity is 20/30 or better OD and OS • Subject willing to use the drop 3-4x a day until Visit 3.	
2.14.	Dispense	Dispense enough artificial tears to last until the next scheduled visit. The subject will be instructed not to use other artificial tears during the dispensing period. Subjects will be scheduled for Visit 3 to ensure the visit is completed 28 to 32 days after V1.	

VISIT 3

Aim for Visit 3 to occur in the afternoon (after 12 PM). The subjects must present to visit 3 wearing their habitual spectacles (if applicable) having used the study drop in both eyes at least 2 times that day.

Visit 3: 30-day Follow-up			
Step	Procedure	Details	[redacted]
3.1.	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
3.2.	Artificial Tear compliance	Confirm the subject used the drops as instructed.	
3.3.	Collection of Study drops	The site will collect and discard the bottle of study eye drops.	
3.4.	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	[redacted]
3.5.	VAS Questionnaire	The subject will respond to the VAS questionnaire	[redacted]
3.6.	PRO Questionnaire	The subject will complete the electronic questionnaires using the Kiosk portal.	[redacted]
3.7.	Preference Question	The subject will complete the electronic preference questions using the Kiosk portal, if applicable.	[redacted]
3.8.	Entrance visual acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]
3.9.	Tear Break up Time	Record the tear film stability (NITBUT), OD and OS, with a Medmont or other topographer.	[redacted]
3.10.	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings. All ocular adverse events must be followed to resolution. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	[redacted]
3.11.	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (1.0 scale units) will be assessed using a more detailed scale for internal purposes only.	[redacted]

FINAL EVALUATION

The final evaluation will ordinarily take place immediately following the last scheduled follow-up visit per the study protocol. It may also take place at any point the subject discontinues the study or is terminated from the study.

Final Evaluation			
Step	Procedure	Details	[redacted]
F.1	Final Exam Form	Indicate if the subject completed the study successfully. If subject discontinued from the study indicate the reason.	
F.2	Exit Distance Visual Acuity	Record the exit distance visual acuity OD, OS, OU with the subject's spectacles or unaided (the same method as used in Visit 1 Baseline entrance distance visual acuity).	[redacted]

7.3. Unscheduled Visits

If, during the investigation, a subject requires an unscheduled visit to the clinical site, the following information will be collected at a minimum:

- Chief complaint prompting the visit. If the reason is an adverse event, the applicable eCRF for the adverse event must be completed and subject record completed as appropriate
- Date and time of the visit and all procedures completed at the unscheduled visit
- Review of adverse event and concomitant medications
- Documentation of any test article dispensed or collected from the subject, if applicable
- Slit lamp findings (using the Slit Lamp Classification Scale)

If the Investigator withdraws a subject from the study, the final study visit case report forms must be completed indicating the reason(s) why the subject was withdrawn. The subject record must be completed documenting the date and primary reason for withdrawal and the study CRA notified.

Any ocular and non-ocular adverse events that are ongoing at the time of the study visit will be followed by the Investigator, within licensure, until they have resolved, returned to pre-treatment status, stabilized, or been satisfactorily explained. If further treatment i.e., beyond licensure is required, the subject will be referred to the appropriate health care provider.

The following information will be collected during an unscheduled visit (when applicable)

Unscheduled Visit			
Step	Procedure	Details	[redacted]
U.1	Chief Complaints	Record the subject's chief complaints for reasons for the unscheduled visit.	
U.2	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
U.3	Entrance VA	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU)	[redacted]

Unscheduled Visit			
Step	Procedure	Details	[redacted]
		with their habitual spectacle correction in place (or unaided if applicable).	
U.4	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	[redacted]
U.5	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings. (All ocular AE's must be followed to resolution) If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops may be instilled.	[redacted]
U.6	Dispensing	Dispensing of additional artificial tear drops, if necessary	
U.7	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	[redacted]

7.4. Laboratory Procedures

Not applicable.

8. SUBJECTS COMPLETION/WITHDRAWAL

8.1. Completion Criteria

Subjects are considered to have completed the study if they:

- Provided informed consent;
- They are eligible;
- Completed all study visits;
- Have not withdrawn/discontinued from the study for any reason described in Section 8.2

8.2. Withdrawal/Discontinuation from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Subject death during the study period
- Subject withdrawal of consent
- Subject not compliant to the study protocol including drop usage schedule
- Subject lost to follow-up
- Subject no longer meets eligibility criteria (e.g. the subject becomes pregnant)
- Subject develops significant or serious adverse events causing discontinuation of study drop
- Subjects who have experienced a Corneal Infiltrative Event (CIE)
- Investigator's clinical judgment regarding the subject safety reasons (that it is in the best interest of the subject to stop treatment)

- Subject not successfully dispensed due to lack of efficacy or safety

For discontinued subjects, the Investigator will:

- Complete the current visit (scheduled or unscheduled)
- Complete the Final Evaluation, indicating the reason that the subject was discontinued from the study
- Collect used test article(s) (brought to the visit) from the subject and discard them, unless otherwise stated in Section 7.2
- Collect all unused test article(s) from the subject

An additional subject may be enrolled if a subject discontinues from the study prematurely.

In cases where a subject is lost to follow-up, every possible effort must be made to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented including two written attempts and a certified letter (or equivalent) as the final attempt.

9. PRE-STUDY AND CONCOMITANT INTERVENTION/MEDICATION

Concomitant medications will be documented during screening and updated during the study. Disallowed medications for this study include: Current habitual use of Prescription Only Medicines for dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).

Concomitant therapies that are disallowed include: Current habitual use of Prescription Only Medicines for dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).

10. DEVIATIONS FROM THE PROTOCOL

Investigator will notify study sponsor upon identification of a protocol deviation. Major protocol deviations must be reported to the sponsor within 24 hours after discovery of the protocol deviation. The Investigator will report deviations per IRB/IEC requirements. All deviations will be tracked and corrective actions implemented as appropriate.

If it becomes necessary for the Investigator to implement a deviation to eliminate an immediate hazard to the trial subject, the Investigator may implement the deviation immediately without notification to the sponsor. Within 24 hours after the implemented deviation, the Investigator must notify and provide the rationale to the Sponsor and, as required, the IEC/IRB.

The prescribed visit window for Visit 2 is 7 +/- 1 days from Visit 1 (Day 0), and for Visit 3 is 30 +/- 2 days from Visit 1. Subjects that complete Visit 2 five (5) days or nine (9) days from Visit 1, or complete Visit 3 twenty-seven (27) or thirty-three (33) days from Visit 1, will be categorized as a minor protocol deviation. Subjects completing Visit 2 at 4 days or earlier or 9 days or later from Visit 1 will be categorized as a major protocol deviation. Subject completing Visit 3 at 27 days or earlier, or 34 days or later from Visit 1 and these subjects or completing Visit 3 at 27 days or earlier will also be categorized as a major

protocol deviation. These subjects with major PDs will be excluded from the primary study analysis.

11. STUDY TERMINATION

The occurrence of one or more Unanticipated Serious Adverse Device Effect (USADE), or any SAE where the relationship to study agent cannot be ruled out, may result in stopping further dispensing of test article. In the event of a USADE or SAE, the Sponsor may unmask the treatment regimen for the subject(s) and will discuss this with the Investigator before any further subjects are enrolled.

The Sponsor will determine when a study will be stopped. The Principal Investigator always has the discretion to initiate stopping the study based on patient safety or if information indicates the study's results are compromised.

JJV reserves the right to terminate the study at any time for any reason. Additionally, the IEC/IRB reserves the right to terminate the study if an unreasonable risk is determined. The study can be terminated by the Principal Investigator at the individual clinical site due to specific clinical observations, if in their opinion, after a discussion with JJV, it is determined that it would be unwise to continue at the clinical site.

JJV (and the IEC/IRB and DMC, if applicable) will evaluate all adverse events. If it is determined that an adverse event presents an unreasonable risk, the investigation, or that part of the investigation presenting the risk, will be terminated, as soon as possible.

Should the study be terminated (either prematurely or as scheduled), the Investigator will notify the IEC/IRB and Regulatory Authority as required by local regulatory requirements.

12. PROCEDURE FOR HANDLING PRODUCT QUALITY COMPLAINTS

A Product Quality Complaint (PQC) refers to any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of test articles after they have been released for clinical trial use.

Potential complaints may come from a variety of sources including but not limited to subjects, clinical research associates (CRA), clinical operations managers (COM), medical monitors, and site personnel, etc. The following are not considered PQCs:

- Subject satisfaction inquiries reported via "Subjective Questionnaires" and "Patient Reported Outcomes (PRO)"
- Clinical test articles that are stored improperly or damaged after receipt at the investigational site
- Artificial tear replacements that occur due to loss/run out
- Damage deemed by clinicians or clinical staff to be caused by handling by the user, and not indicative of a quality deficiency, only in situations where there is no deficiency alleged by the subject

Within 24 hours of site personnel becoming aware that a PQC has occurred, the PQC must be recorded in the EDC system, which will trigger an automatic email notification to the

appropriate COM/CRA and Clinical QA representative. In cases where the EDC system in use is not configured to send automatic notifications or when an EDC system is not used, the COM/CRA is responsible for notifying Clinical QA upon discovery that a PQC has occurred.

Upon receipt of the EDC notification, the COM/CRA will contact the study site to collect additional information which will include:

- Date the complaint was received/recorded in the EDC System (Date of Sponsor Awareness)
- Who received the complaint
- Study number
- Clinical site information (contact name, site ID, telephone number)
- Lot number(s)
- Unique Subject Identifier(s)
- Indication of who first observed complaint (site personnel or subject)
- OD/OS indication, along with whether the drops were inserted
- Any related AE number, if applicable
- Detailed complaint description (scheduled/unscheduled visit, symptoms, resolution of symptoms, etc.)
- Eye Care Provider objective (slit lamp) findings if applicable
- Confirmation of product availability for return (and tracking information, if available), or rationale if product is not available for return [redacted]

Once a complaint is received, it will be assessed by the COM, CRA, or trained site personnel to determine if it is an Adverse Event/Serious Adverse Event (AE/SAE). If the complaint results in an AE/SAE, the COM/CRA, or trained site personnel will follow Section 13 of this protocol. If the AE/SAE was potentially the result of a product quality related deficiency, these procedures also applies and will be executed in parallel.

In some cases, a PQC form may be generated in EDC by the site in error. In this event, the PQC forms will be marked "Intentionally Left Blank" or "ILB". Justification for ILB must be documented.

13. ADVERSE EVENTS

13.1. Definitions and Classifications

Adverse Event (AE) – An AE is "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.
Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to investigational medical devices."[1]

An AE includes any condition (including a pre-existing condition) that:

1. Was not present prior to the study, but appeared or reappeared following initiation of the study
2. Was present prior to the study but worsened during the study. This would include any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states
3. Pregnancy must be documented as an adverse event and must be reported to the clinical monitor and to the Sponsor immediately upon learning of the event

Serious Adverse Event (SAE) – An SAE is any untoward medical occurrence that:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (e.g., a sight threatening event, a significant persistent or permanent change, impairment, damage, or disruption to the subject's body)
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent permanent damage (the use of the test article resulting in a condition which requires medical or surgical intervention to preclude permanent impairment of the body structure or a body function). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Diagnoses and conditions that are considered Ocular Serious Adverse Events include, but not limited to:

- Microbial Keratitis (MK)
- Iritis (including cells in the anterior chamber)
- Permanent decrease in best spectacle corrected visual acuity equivalent to 2 acuity lines or greater
- Central Corneal Opacity
- Central Corneal Neovascularization
- Uveitis
- Endophthalmitis
- Hypopyon
- Hyphemia
- Penetration of Bowman's Membrane
- Persistent Epithelial Defect
- Limbal cell Damage leading to Conjunctivalization

Significant Adverse Events – Those events that are usually symptomatic and warrant discontinuation (temporary or permanent) of the test article (excluding Serious Adverse Events).

Diagnoses and conditions that are considered Ocular Significant Adverse Events include, but not limited to the following:

- Significant Infiltrative Events (SIE)
- Keratoconjunctivitis (toxic or infectious)
- Chemical Keratitis

- Any Temporary Loss of >2 Lines of BSCVA
- Other Grade 3 or higher corneal findings, such as abrasions or edema
- Corneal events - e.g. Epidemic Keratoconjunctivitis (EKC)
- Asymptomatic Corneal Scar
- Any corneal event which necessitates temporary lens discontinuation >2 weeks

Non-Significant Adverse Events – Those conditions that are usually asymptomatic and usually do not warrant discontinuation (temporary or permanent) of the test article. However, the Investigator may choose to treat as a precautionary measure.

Diagnoses and conditions that are considered Ocular Non-Significant Adverse Events include, but not limited to the following:

- Non-signifiant Infiltrative Event (NSIE)
- Papillary Conjunctivitis
- Corneal abrasions
- Superficial Punctate Keratitis (SPK)
- Conjunctivitis: Bacterial, Viral, Allergic
- Blepharitis
- Meibomianitis
- Contact Dermatitis
- Localized Allergic Reactions or infections
- Temporary visual disturbances (blurriness)
- Any corneal event not explicitly defined as serious or significant adverse event, which necessitates temporary discontinuation of the drops <2 weeks

Adverse Device Effect (ADE) – An ADE is an "adverse event related to the use of an investigational medical device.
Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device."[1]

Unanticipated Adverse Device Effect (UADE) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the test article, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, Investigator's Brochure or protocol, or any other unanticipated serious problem associated with the test article that relates to the rights, safety and welfare of subjects.

13.2. Assessing Adverse Events

In conjunction with the medical monitor, the Investigator will evaluate adverse events to ensure the events are categorized correctly. Elements of categorization will include:

- Seriousness/Classifications (see definition in Section 13.1)
- Causality or Relatedness – i.e. the relationship between the test article, study treatment or study procedures and the adverse event (not related; unlikely related; possibly related; related - see definition in Section 13.2.1)

- Adverse Event Severity – Adverse event severity is used to assess the degree of intensity of the adverse event (mild; moderate; severe for all events - see definition in Section 0)
- Outcome – not recovered or not resolved; recovering or resolving; recovered or resolved with sequelae; recovered or resolved; death related to adverse event; unknown
- Actions Taken – none; temporarily discontinued; permanently discontinued; other

13.2.1. Causality Assessment

Causality Assessment – A determination of the relationship between an adverse event and the test article. The test article relationship for each adverse event should be determined by the investigator using these explanations:

- Not Related- An adverse event that is not related to the use of the test article, study treatment or study procedures
- Unlikely Related – An adverse event for which an alternative explanation is more likely, e.g. concomitant treatment, concomitant disease(s), or the relationship of time suggests that a causal relationship is not likely
- Possibly Related – An adverse event that might be due to the use of the test article, or to the study treatment or study procedures. An alternative explanation, e.g. concomitant treatment, concomitant disease(s), is inconclusive. The relationship in time is reasonable. Therefore, the causal relationship cannot be excluded
- Related – An adverse event that is listed as a possible adverse effect (device) or adverse reaction (drug) and cannot be reasonably explained by an alternative explanation, e.g. concomitant treatment of concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by de-challenge and re-challenge

13.2.2. Severity Assessment

Severity Assessment – A qualitative assessment of the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article, study treatment or study procedure relationship or seriousness of the event and should be evaluated according to the following scale:

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

13.3. Documentation and Follow-Up of Adverse Events

The recording and documenting of adverse events (ocular and non-ocular) begins when the subjects are exposed to the test article, study treatment or study procedure. Adverse events reported before the use of test article, start of study treatment, or study procedures will be recorded as medical history. However, if the condition deteriorates at any time during the study it will be recorded and reported as an AE. Untoward medical events reported after the subject's exit from the study will be recorded as adverse events at the discretion of the Investigator.

Upon finding an adverse event, the Principal Investigator will document the condition in the subject record and in the eCRFs. He/she will complete the Adverse Event /eCRF.

Complete descriptions of all adverse events must be available in the subject record. All Adverse Events including local and systemic reactions not meeting the criteria for "serious adverse events" shall be captured on the appropriate case report form or electronic data system. All adverse events occurring while the subject is enrolled in the study must be documented appropriately regardless of relationship.

It is the Investigator's responsibility to maintain documentation of each reported adverse event. All adverse events will be followed in accordance with applicable licensing requirements. Such documentation will include the following:

- Adverse event (diagnosis not symptom)
- Drawings or photographs (where appropriate) that detail the finding (e.g., size, location, and depth, etc.)
- Date the clinical site was notified
- Date and time of onset
- Date and time of resolution
- Adverse event classification, severity, and relationship to test articles, as applicable
- Treatment regimen instituted, including concomitant medications prescribed, in accordance with applicable licensing requirements
- Any referral to another health care provider if needed
- Outcome, ocular damage (if any)
- Likely etiology
- Best corrected visual acuity at the discovery of the event and upon conclusion of the event

In addition, if an infiltrate(s) is present, he/she will complete the Corneal Infiltrate Assessment eCRF. Where necessary, a culture of the corneal lesion will be collected to determine if the infection is microbial in nature. If cultures are collected, the date of culture collection and laboratory utilized will be recorded.

Changes in the severity of an AE shall be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode. Changes in the assessment of relationship to the Test Article shall also be clearly documented.

Subjects who present with an adverse event shall be followed by the Investigator, within licensure, until all signs and symptoms have returned to pre-treatment status, stabilized, or been satisfactorily resolved. If further treatment beyond licensure is required, the patient will be referred to the appropriate health care provider. The Investigator will use his/her clinical judgment as to whether a subject reporting with an adverse event will continue in the study. If a subject is discontinued from the study, it will be the responsibility of the Investigator to record the reason for discontinuation. The Investigator will also document the adverse event appropriately and complete the Adverse Event eCRF. Any subjects with ongoing adverse events related to the test article, study treatment or study procedures, as of the final study visit date, should be followed to resolution of the adverse event or until referral to an appropriate health care provider, as recommended by the Investigator. Non-

ocular adverse events that are not related to the test article, study treatment, or study procedures may be recorded as "ongoing" without further follow-up.

13.4. Reporting Adverse Events

The Investigator will notify the Sponsor of an adverse event by e-mail, facsimile, or telephone as soon as possible and no later than 24 hours from discovery for any serious /significant adverse events, and 2 days from discovery for any non-significant adverse event. In addition, a written report will be submitted by the Principal Investigator to the IEC/IRB according to their requirements (Section 13.4.2). The report will comment whether or not the adverse event was considered to be related to the test article, study treatment or study procedures.

13.4.1. Reporting Adverse Events to Sponsor

Serious/Significant Adverse Events
The Investigator will inform the sponsor of all serious/significant adverse events occurring during the study period as soon as possible by e-mail, fax, or telephone, but no later than 24 hours following discovery of the event. The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious/significant adverse event must be followed up and all outcomes must be reported.

When medically necessary, the Investigator may break the randomization code to determine the identity of the treatment that the subject received. The Sponsor and study monitor should be notified prior to unmasking the test articles.

In the event of a serious/significant adverse event, the Investigator must:

- Notify the Sponsor immediately
- Obtain and maintain in the subject's records all pertinent medical information and medical judgment for colleagues who assisted in the treatment and follow-up of the subject
- Provide the Sponsor with a complete case history which includes a statement as to whether the event was or was not related to the use of the test article
- Notify the IEC/IRB as required by the IEC/IRB reporting procedure according to national regulations

Unanticipated (Serious) Adverse Device Effect (UADE)
In the event of an Unanticipated (Serious) Adverse Device Effect (UADE), the Investigator will submit a report of the UADE to the Sponsor and IEC/IRB as soon as possible, but no later than 24 hours after the Investigator first learns of the effect. This report is in addition to the immediate notification mentioned above.

The Sponsor must conduct an evaluation of the UADE and must report the results of the evaluation to FDA, the IEC/IRB and participating Investigators within 10 working days after the Sponsor first receives notification of the effect.

Non-Serious Adverse Events
All non-serious adverse events, including non-serious adverse device effects, will be reported to the sponsor by the Investigator no later than 2 days from discovery.

13.4.2. Reporting Adverse Events to the Responsible IEC/IRB and Health Authorities

Adverse events that meet the IEC/IRB requirements for reporting must be reported within the IEC/IRB's written guidelines. Each clinical site will refer to and follow any guidelines set forth by their Approving IEC/IRB. Each clinical site will refer to and follow any guidelines set forth by their local governing Health Authorities.

The Sponsor will report applicable Adverse Events to the local health authorities according the written guidelines, including reporting timelines.

13.4.3. Event of Special Interest

None.

13.5. Reporting of Pregnancy

Subjects reporting pregnancy (by self-report) during the course of the study will be discontinued after the event is recorded as an Adverse Event. Once discontinued, pregnant participants and their fetuses will not be monitored for study related purposes. At the Investigator's discretion, the study participant may be followed by the Investigator through delivery. However, this data will not be collected as part of the clinical study database. Pregnant participants are not discontinued from contact lens or solution related studies for safety concerns, but due to general concerns relating to pregnancy and contact lens use. Specifically, pregnant women are discontinued due to fluctuations in refractive error and/or visual acuity that occur secondary to systemic hormonal changes, and not due to unforeseen health risks to the mother or fetus.

14. STATISTICAL METHODS

14.1. General Considerations

Statistical Analysis will be undertaken by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be implemented in this clinical trial is outlined below. More details will be provided in the stand-alone Statistical Analysis Plan (SAP). The SAP will be finalized and signed prior to the database lock.

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher[10]. Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

14.2. Sample Size Justification

The sample size was calculated to test for non-inferiority of the Test relative to Control eye drops with respect to the ocular comfort score using VAS with a minimum power of 85% and a two-sided type I error of 0.05. Assuming a difference between the Test and Control of 20, a common standard deviation (SD) of 35, the estimated sample size for non-

inferiority was 56 per treatment group using two-sample t-test. The sample size calculation was performed using the SAS procedure PROC POWER. The common standard deviation considered was based on results from [redacted] in which the estimated standard deviation of change in ocular end of day comfort from baseline at 30-day in the control group was estimated to be 2.53 in a VAS scale from 0 to 10 [redacted] We increased the standard deviation by one unit in case more variation will be observed in the Test group. Therefore, the standard deviation used in the sample calculation was 35 in a VAS scale from 0 to 100 (35 = 10*(2.5 + 1)).

The plan is to enroll 150 eligible subjects (60 per arm) with a target completion of 112 (56 per arm). During the enrollment period, the subject dropout rate will be closely monitored, if unexpectedly high dropout rate is observed (>10%) in certain arm(s), the targeted total enrollment number might be increased accordingly in order to ensure a minimum of 56 subjects per group to complete the 1-month follow-up.

14.3. Analysis Populations

The following analysis populations will be used in the analysis and presentation of the data.

Safety Population:
All subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation for safety endpoints should be recorded (e.g. slit lamp findings, ocular symptoms, etc.).

Intent-to-Treat (ITT) Population:
All randomized subjects regardless of actual treatment and subsequent withdrawal from study or deviation from protocol. Subject will be analyzed as per randomized treatment.

Per-Protocol (PP) Population:
All subjects who have successfully completed all visits and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database lock. Justification of excluding subjects with protocol deviations from the Per-Protocol Population set will be documented in a memo to file. Per Protocol will be the primary analysis population.

14.4. Level of Statistical Significance

All planned analysis will be conducted with an overall type I error rate of 5%. Unless otherwise specified, all statistical tests will be 2-sided.

14.5. Primary Analysis

Ocular Comfort (VAS) Score:
Ocular comfort scores will be analyzed using a linear mixed model for repeated measures to test for the difference between the Test and Control eye drops. The regression model will include treatment group (Test, Control), time (0, 7-Day and 30-Day) and group by time interaction as fixed effect factors; and investigational site as random effect. Age and gender will be included in the model when appropriate. The correlation between measurements from the same subject across time will be modeled using unstructured (UN) variance-covariance matrix. If the estimation algorithm does not converge, then a Compound Symmetry matrix (CS) will be used. The log-likelihood ratio test will be used to test for the

homogeneity between the residual covariance structures across treatment groups. The Kenward and Roger method [11] will be used to calculate the denominator degree of freedom.

Hypothesis Testing:
The null and alternative hypotheses for non-inferiority of Test relative to Control are as follows:

$$H_0: \Delta \leq -20$$
$$H_A: \Delta > -20,$$

where Δ is the difference between treatment groups in mean change from baseline at 30-Day follow-up (Test minus Control). The non-inferiority test will be based on the least square mean change difference and corresponding 95% confidence interval from the final model. The lower bound of the 95% confidence interval will be compared to the non-inferiority margin of -20. If the lower bound is greater than -20, the null hypothesis will be rejected, and the Test will be considered non-inferior to Control. The primary analysis will be conducted on the Per-Protocol Population. As sensitivity analysis will be conducted on the ITT Population.

14.6. Secondary Analysis

Corneal Staining (Grade 2 or higher):
Corneal staining response using FDA grading scale (i.e. Grade 0 = None, Grade 1 = Trace, Grade 2 = Mild, Grade 3 = Moderate and Grade 4 = Severe) will be first categorized into a binary outcome as 1 if any grade 2 or higher corneal staining otherwise 0. Events occurring during an unscheduled visit will be counted in the subsequent visit. For example, if a Grade 2 corneal staining was reported at an unscheduled visit between Visit 1 and Visit 2, it would be counted in Visit 2. Eyes with multiple reports will be counted only once at each visit for the analysis purpose. The binary outcome will be then analyzed using a generalized linear mixed model for binary data. The regression model will include treatment group (Test, Control), time (0, 7-Day and 30-Day) and group by time interaction as fixed effect factors; and investigational site and subject as random effects (G-side). Baseline values, age and gender will be included in the model as fixed covariates when appropriate. The correlation between measurements from the same subject/eye across time will be modeled using UN variance-covariance matrix (R-side). If the estimation algorithm does not converge, then a compound symmetry structure (CS) will be used. The Kenward and Roger method [11]will be used to calculate the denominator degree of freedom.

Hypothesis Testing:
The null and alternative hypotheses for no difference of Test relative to Control are as follows:

$$H_0: OR = 1$$
$$H_A: OR \neq 1,$$

where OR is odds ratio of having a Grade 2 or higher corneal staining in the Test group over the Control group.

Comparison between the Test and Control will be conducted at each follow-up visit and across all visits. The test for no difference will be based on the estimated OR and corresponding 95% confidence interval from the final model. The null hypothesis will be rejected in favor of the alternative if 1 does not fall within the 95% confidence interval of OR. The corneal staining analysis will be conducted on the Safety Population.

Overall Quality of Vision Score:
Overall quality of vision will be analyzed using the same statistical model described in the primary analysis. Comparisons between Test and Control will be carried using t-tests on least square mean differences of change in quality of vision from baseline at 7-Day and 30-Day follow-up. The overall quality of vision analysis will be conducted on the Per-Protocol Population.

Subject reported Ocular symptoms (yes/No)
Reported ocular symptoms, problems or complaints (0 = No, 1 = Yes) at any visit will be analyzed using the same method described above for corneal staining. The reported ocular analysis will be conducted on the Safety Population.

14.7. Other Exploratory Analyses

No exploratory analyses are planned for this study. Further analysis will be conducted at the discretion of the study responsible clinician at the end of the study if necessary.

14.8. Interim Analysis

No interim analysis is planned in this study.

14.9. Procedure for Handling Missing Data and Drop-Outs

Missing or spurious values will not be imputed as the number of missing values is expected to be low. The count of observed values will be included in the summary tables and listings.

Subject dropout is expected to be one of the main reasons of missing data in this clinical trial. Past clinical trials don't provide the evidence that subject dropout is systematic or not-at-random. To evaluate the impact of missing data, a sensitivity analysis will be conducted using multiple imputation methods.

14.10. Procedure for Reporting Deviations from Statistical Plan

The analysis will be conducted according to that specified in the above sections. There are no known reasons for which it is planned to deviate from these analysis methods. If for any reason a change is made, the change will be documented in the study report along with a justification for the change.

15. DATA HANDLING AND RECORD KEEPING/ARCHIVING

15.1. Electronic Case Report Form/Data Collection

The data for this study will be captured on electronic case report forms (eCRFs) using an EDC system (Bioclinica). An authorized data originator will enter study data into the eCRFs using the EDC system. Data collected on equipment that is not captured in EDC

will be formatted to the specification of the JJV database manager and sent to JJV for analysis.

External Date Sources for this study include: Not Applicable

The clinical data will be recorded on dedicated eCRFs specifically designed to match the study procedures for each visit. Once completed, the eCRFs will be reviewed for accuracy and completeness and signed by the Investigator. The sponsor or sponsor's representatives will be authorized to gain access to the subject recordation for the purposes of monitoring and auditing the study.

Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection. Data will be transmitted from the clinical site to a secure central database as forms are completed or updated, ensuring information accuracy, security, and confidentiality. After the final database lock, the Investigator will be provided with Individual Patient Profiles (IPP) including the full audit trail on electronic media in PDF format for all of the study data. The IPP must be retained in the study files as a certified copy of the source data for the study.

The content and structure of the eCRFs are compliant with ISO14155:2011.[1]

15.2. Subject Record

At a minimum, subject record should be available for the following:

- subject identification
- eligibility
- study identification
- study discussion
- provision of and date of informed consent
- visit dates
- results of safety and efficacy parameters as required by the protocol
- a record of all adverse events
- follow-up of adverse events
- medical history and concomitant medication
- test article receipt/dispensing/return records
- date of study completion
- reason for early discontinuation of test article or withdrawal from the study, if applicable

The subject record is the eCRF or an external record. The author of an entry in the subject record must be identifiable. The first point of entry is considered to be the source record.

Adverse event notes must be reviewed and initialed by the Investigator.

16. DATA MANAGEMENT

16.1. Access to Source Data/Document

The Investigator/Institution will permit trial-related monitoring, audits, IEC/IRB review and regulatory inspection(s) by providing direct access to source data/documents. Should

the clinical site be contacted for an audit by an IEC/IRB or regulatory authority, JJV must be contacted and notified in writing within 24 hours.

16.2. Confidentiality of Information

Information concerning the investigational product and patent application processes, scientific data or other pertinent information is confidential and remains the property of JJV. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that JJV will use information developed in this clinical study in connection with the development of the investigational product and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

16.3. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data, include the selection of qualified investigators and appropriate clinical sites and review of protocol procedures with the Principal Investigator. The Principal Investigator, in turn, must ensure that all Sub-Investigators and clinical site personnel are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study article.

Training on case report form completion will be provided to clinical site personnel before the start of the study. The Sponsor will review case report forms for accuracy and completeness remotely during the conduct of the study, during monitoring visits, and after transmission to data management. Any data discrepancies will be resolved with the Investigator or designee, as appropriate.

Quality Assurance representatives from JJV may visit clinical sites to review data produced during the study and to access compliance with applicable regulations pertaining to the conduct of clinical trials. The clinical sites will provide direct access to study-related source data/documents and reports for the purpose of monitoring and auditing by JJV and for inspection by local and regulatory authorities.

17. MONITORING

The study monitors will maintain close contact with the Principal Investigator and the Investigator's designated clinical site personnel. The monitor's responsibilities will include:

- Ensuring that the investigation is being conducted according to the protocol, any subsequent amendments, and regulatory requirements are maintained
- Ensuring the rights and wellbeing of subjects are protected
- Ensuring adequate resources, including facilities, laboratories, equipment, and qualified clinical site personnel
- Ensuring that protocol deviations are documented with corrective action plans, as applicable
- Ensuring that the clinical site has sufficient test article and supplies
- Clarifying questions regarding the study
- Resolving study issues or problems that may arise

- Reviewing of study records and source documentation verification in accordance with the monitoring plan

18. ETHICAL AND REGULATORY ASPECTS

18.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. Subjects will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

18.2. Investigator Responsibility

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the signed agreement, the investigational plan, Section 4 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory 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 study subjects are protected, consistent with the principles of the Declaration of Helsinki 64th WMA General Assembly 2013[3] and that the clinical study data are credible. The Investigator must maintain clinical study files in accordance with Section 8 of the ICH E6 guidelines on Good Clinical Practice (GCP),[2] and applicable regulatory requirements.

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

Before the start of the study, the Investigator (or Sponsor when applicable) will provide the IEC/IRB with current and complete copies of the following documents (where applicable):

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruitment materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's curriculum vitae, clinical licenses, or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study, the Investigator (or Sponsor when applicable) will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruitment materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)
- Reports of adverse events that are serious, unanticipated, and associated with the test articles, according to the IRB's requirements
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Major protocol deviations as required by the IEC/IRB
- Report of deaths of subjects under the Investigator's care
- Notification if a new Investigator is responsible for the study at the clinical site
- Any other requirements of the IEC/IRB

For protocol amendments that increase subject risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will review and reapprove this clinical study. This request should be documented in writing.

At the end of the study, the Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion. Documentation of this notification must be retained at the clinical site and a copy provided to the CRO or Sponsor as applicable.

18.4. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent is in accordance with principles that originated in the Declaration of Helsinki[3], current ICH[2] and ISO 14155[1] guidelines, applicable regulatory requirements, and Sponsor Policy.

Before entry into the study, the Investigator or an authorized member of the clinical site personnel must explain to potential subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

18.5. Privacy of Personal Data

The collection, processing and disclosure of personal data and medical information related to the Study Subject, and personal data related to Principal Investigator and any clinical site personnel (e.g., name, clinic address and phone number, curriculum vitae) is subject to compliance with the Health Information Portability and Accountability Act (HIPAA)[12] in the United States and other applicable personal data protection and security laws and regulations. Appropriate measures will be employed to safeguard these data, to maintain the confidentiality of the person's related health and medical information, to properly inform the concerned persons about the collection and processing of their personal data, to grant them reasonable access to their personal data and to prevent access by unauthorized persons.

All information obtained during the course of the investigation will be regarded as confidential. All personal data gathered in this trial will be treated in strictest confidence by Investigators, monitors, Sponsor's personnel and IEC/IRB. No data will be disclosed to any third party without the express permission of the subject concerned, with the exception of Sponsor personnel (monitor, auditor), IEC/IRB and regulatory organizations in the context of their investigation related activities that, as part of the investigation will have access to the CRFs and subject records.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
The Sponsor ensures that the personal data will be:

- processed fairly and lawfully
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable 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 study subjects confidential.

19. STUDY RECORD RETENTION

In compliance with the ICH/GCP guidelines,[2] the Investigator/Institution will maintain all CRFs and all subject records that support the data collected from each subject, as well as all study documents as specified in ICH/GCP[2] and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or instructed by the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.
If the Investigator has a question regarding retention of study records, he/she should contact JJV.

20. FINANCIAL CONSIDERATIONS

Remuneration for study services and expenses will be set forth in detail in the Clinical Research Agreement. The Research Agreement will be signed by the Principal Investigator and a JJV management representative prior to study initiation.

JJV reserves the right to withhold remuneration for costs associated with protocol violations such as:

- Continuing an ineligible subject in the study
- Scheduling a study visit outside the subject's acceptable visit range

JJV reserves the right to withhold final remuneration until all study related activities have been completed, such as:

- Query resolution
- Case Report Form signature
- Completion of any follow-up action items

21. PUBLICATION

This study will be registered on ClinicalTrials.gov based on the following: This confirmatory study meets the registration requirements in [redacted]

22. REFERENCES

1. ISO14155:2011: Clinical investigation of Medical Devices for Human Subjects-Good Clinical Practice. Available at: https://www.iso.org/standard/45557.html

2. International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

3. Declaration of Helsinki - Ethical principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

4. United States (US) Code of Federal Regulations (CFR) Available at : https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR

5. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of Diagnosed Dry Eye Disease in the United States Among Adults Aged 18 Years and Older. *American Journal of Ophthalmology.* 2017;182:90-98.

6. Pearce E, Jobson A, Tandon S, KJ. B. Dry Eye Questionnaires: A comparison of the Responses Made to Visual Analogue Scale Questionnaires With Those made to Category Based Questionnaires. *IOVS.* 2005;46(13):4452.

7. Klimek L, Bergmann K-C, Biedermann T, et al. Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). *Allergo J Int.* 2017;26(1):16-24.

8. ISO 11980:2012 Ophthalmic optics- Contact Lenses and Contact Lens Care Products.- Guidance for Clinical Investigations. Available at: https://www.iso.org/standard/61825.html

9. Versura P, Fresina M, Campos EC. Ocular surface changes over the menstrual cycle in women with and without dry eye. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2007;23(7):385-390.

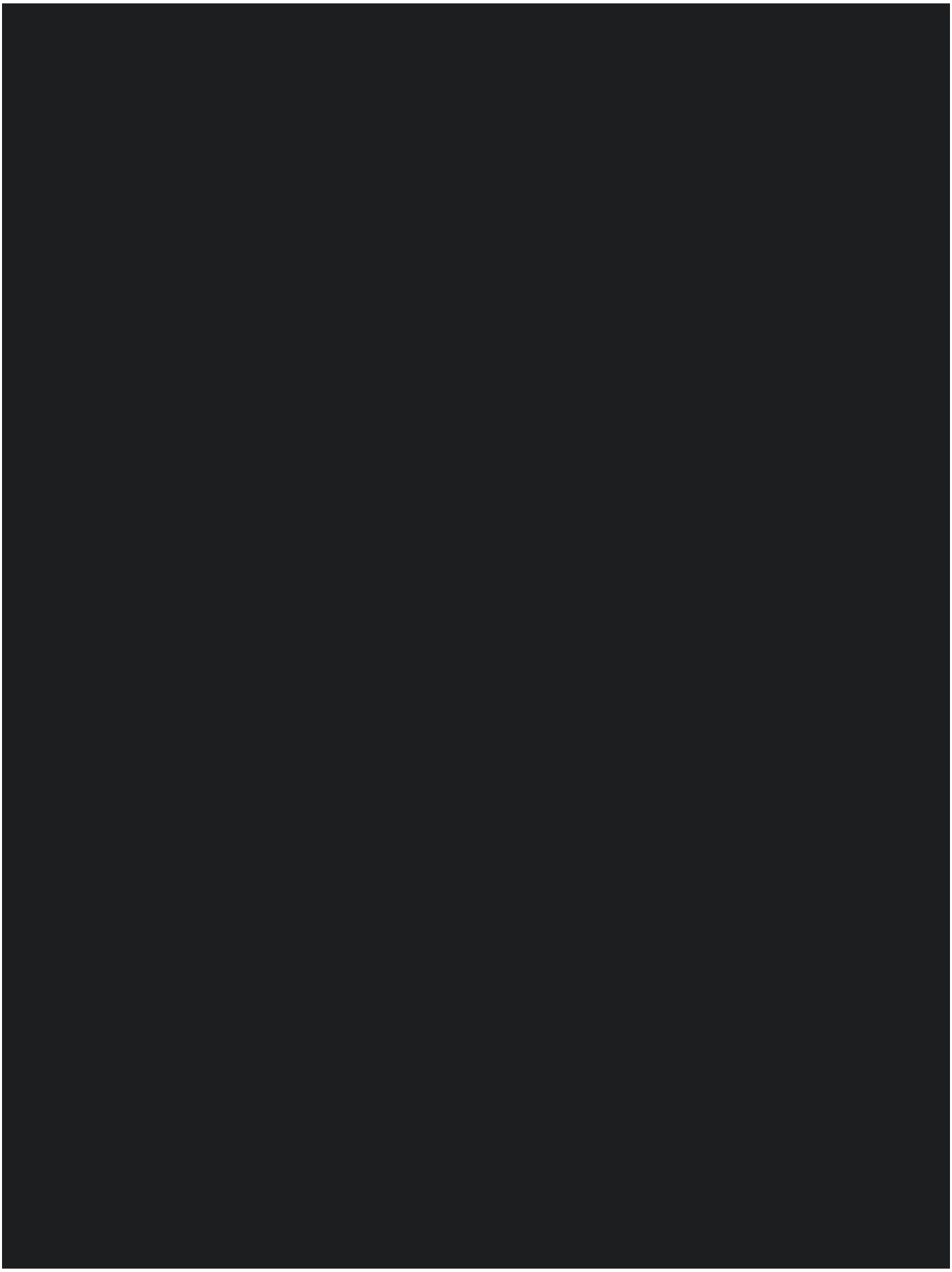
10. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.

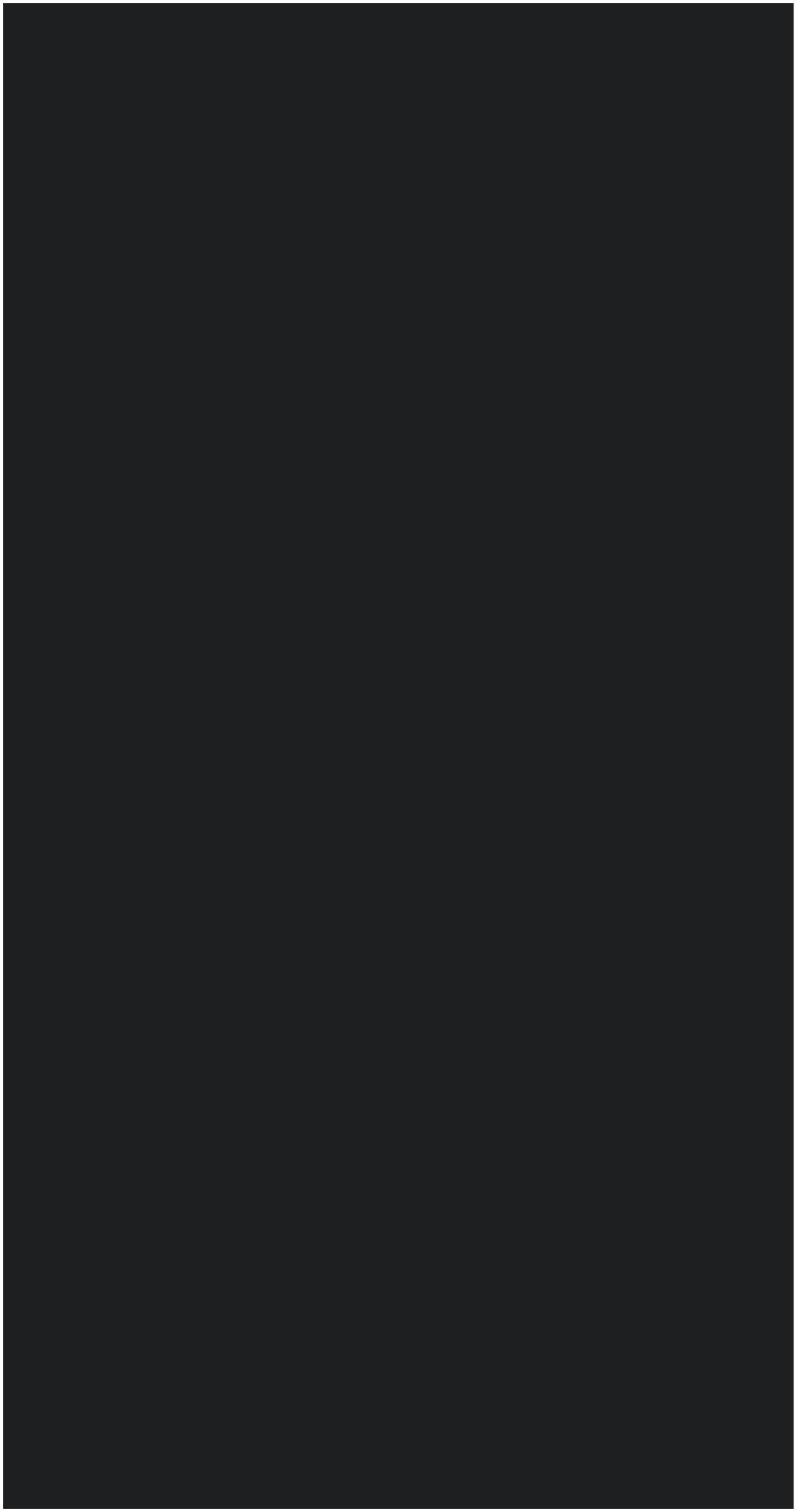
11. Kenward MG, Roger JH. An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics & Data Analysis.* 2009;53(7):2583-2595.

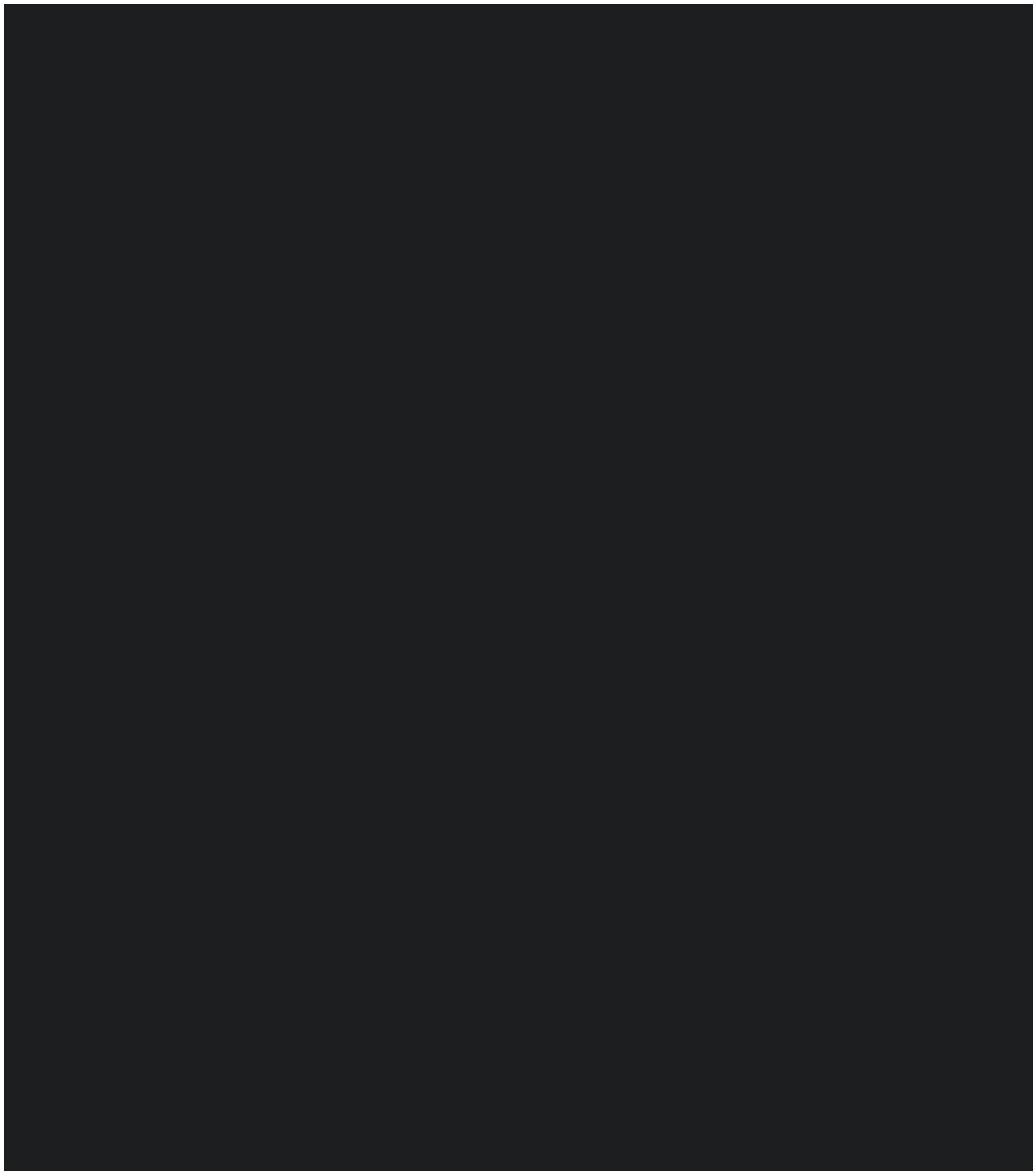
12. Data Protection Act. Available at: http://www.legislation.gov.uk/ukpga/1998/29/contents

APPENDIX A: PATIENT REPORTED OUTCOMES (STUDY QUESTIONNAIRES)

[redacted]







APPENDIX B: PATIENT INSTRUCTION GUIDE

Patient Instruction Guide will be provided separately.

APPENDIX C: PACKAGE INSERT (APPROVED PRODUCT)

blink® Tears

Lubricating Eye Drops

Drug Facts

Active Ingredient — **Purpose**

Polyethylene Glycol 400 0.25% . . . . . Eye lubricant

Uses ■ For the temporary relief of burning, irritation, and discomfort due to dryness of the eye or exposure to wind or sun.

■ May be used as a protectant against further irritation.

Warnings

■ For external use only.

■ To avoid contamination, do not touch tip of container to any surface. Replace cap after using.

■ Do not use if solution changes color or becomes cloudy.

Stop use and ask a doctor if:

You experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours.

Keep out of the reach of children.

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

Directions

Instill 1 or 2 drops in the affected eye(s) as needed or as directed by your eye care professional.

Inactive Ingredients

Boric Acid; Calcium Chloride; Magnesium Chloride; Potassium Chloride; Purified Water; Sodium Borate; Sodium Chloride; Sodium Chlorite (OcuPure® brand) as a preservative; Sodium Hyaluronate.

Other Information

Use only if tape seals on top and bottom flaps are intact.

RETAIN THIS CARTON FOR FUTURE REFERENCE.

Discard solution 90 days after opening

Product of China made in accordance with US FDA guidelines

No. 93286BT

AM60870US12C

9587X

Revision Date: 07/2018

APPENDIX D: MEDMONT ASSESSMENT PROCEDURE

[redacted]

Page **1** of **4**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]
[redacted]

[redacted] [redacted]
[redacted]

[redacted] [redacted]
[redacted]

[redacted] [redacted]
[redacted]

[redacted]

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

Page **4** of **4**

[redacted]

APPENDIX E: [redacted]

- [redacted] Expanded Corneal Staining assessment
- [redacted] Subject reported Ocular Symptoms/Problems
- [redacted] Biomicroscopy Scale
- [redacted] Distance and Near Visual Acuity Evaluation
- [redacted] Patient Reported Outcomes

[redacted] EXPANDED CORNEAL STAINING ASSESSMENT

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] SUBJECT REPORTED OCULAR SYMPTOMS/PROBLEMS

[redacted]

[redacted] BIOMICROSCOPY SCALE

[redacted]

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

Page 1 of 5

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] DISTANCE AND NEAR VISUAL ACUITY

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] PATIENT REPORTED OUTCOMES

[redacted]

PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE

Protocol Number and Title: CR-6328 Clinical Evaluation of an Investigational Lipid Drop in Non-contact Lens Wearing Patients

Version and Date: 4.0 13 August 2019

I have read and understand the protocol specified above and agree on its content.

I agree to conduct this study according to ISO 14155,[1] GCP and ICH guidelines, [2] the Declaration of Helsinki, [3] United States (US) Code of Federal Regulations (CFR),[4] and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations. The Principal Investigator is responsible for ensuring that all clinical site personnel, including Sub-Investigators adhere to all ICH[2] regulations and GCP guidelines regarding clinical trials during and after study completion.

I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I am responsible for ensuring that all clinical site personnel including Sub-Investigators adhere to all ICH[2] regulations and GCP guidelines regarding clinical trials during and after study completion.

All clinical site personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all clinical site personnel involved in the conduct of this study are informed about their obligations in meeting the above commitments.

I shall not disclose the information contained in this protocol or any results obtained from this study without written authorization.

Principal Investigator:

_____ _____

Signature Date

_____

Name and Professional Position (Printed)

Institution/Site:

_____

Institution/Site Name

_____

Institution/Site Address