Clinical Study Protocol
Johnson & Johnson Vision Care, Inc.

Clinical Evaluation of a Multidose Preservative-free Lubricating Eye Drops Contained in Novelia® Eye Dropper in Non-Contact Lens Wearing Patients

Protocol CR-6502

Version: 3.0

Date: 25 April 2023

Investigational Products: Investigational Lubricating Eye Drop ([redacted]) in a Novelia® Multidose Eyedropper

Approved Product: Blink® Tears lubricating eyedrops

Keywords: 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 clinical trial will be conducted in compliance with ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice[1], International Council for Harmonization Good Clinical Practice E6(R2) (ICH GCP)[2] and the Declaration of Helsinki[3] as applicable.

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PROTOCOL TITLE, NUMBER, VERSION AND DATE

Title: Clinical Evaluation of a Multidose Preservative-free Lubricating Eye Drops Contained in Novelia® Eye Dropper in Non-Contact Lens Wearing Patients
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SPONSOR NAME AND ADDRESS

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

MEDICAL MONITOR

The Medical Monitor must be notified by the clinical institution/site by e-mail 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 signatures below constitutes the approval of this protocol and the attachments and provide 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], ISO 14155:2020[1], ICH GCP E6(R2)[2] and the Declaration of Helsinki.[3]

Author & Study Responsible Clinician	*See Electronic Signature Report* [redacted]	DATE
Clinical Operations Manager	*See Electronic Signature Report* [redacted]	DATE
Biostatistician	*See Electronic Signature Report* [redacted]	DATE
Data Management	*See Electronic Signature Report* [redacted]	DATE
Medical Safety Officer	*See Electronic Signature Report* [redacted]	DATE
Approver	*See Electronic Signature Report* [redacted]	DATE
Approver	*See Electronic Signature Report* [redacted]	DATE

CHANGE HISTORY

Version	Originator	Description of Change(s) and Section Number(s) Affected	Justification for Change	Date
1.0	[redacted]	Original Protocol	N/A	21 November 2022
2.0	[redacted]	• Added ICH E6(R2) on the title page, and in all Signature pages • Added: ADR- Adverse Drug Reaction in Glossary • Removed ADE, UADE and USADE from the glossary • Added SROS, NIBUT to the Glossary • Added "*except for artificial tears"* for exclusion criteria number 8. • Changed the timing of Visit 2 from 7±1 days to 14±2 days throughout the document. • Removed UADE from Synopsis, Study Termination • Added: The indications for the investigational eyedrops are consistent with 21 CFR Part 349.60 pertaining to the demulcent eyedrops as per the FDA OTC monograph in "Indications" Section 1.2. • Changed artificial tears to control eye drops in Section 1.4 • Clarified that the subject may return up to 1 additional baseline visit in section 5.1 • Added "Subjects will be instructed not to use other artificial tears during the dispensing period." In Detailed study procedure Section 1.24. • Added: Definition of ADR in the adverse event section in Section 13.1. • Removed ADE and UADE definitions from Section 13.1 • Removed UADE reporting guidelines from Section 13.4.1 • Added links in Section 22, References • Corrected typos throughout	Modifications made to be consistent as per ICH requirements	14 February 2023

Version	Originator	Description of Change(s) and Section Number(s) Affected	Justification for Change	Date
3.0	[redacted]	• Added clarification and details behind the single masked nature of the study in Sections 5.2 and 5.3 • Improved Major and Minor Deviation language describing some examples on Table 7, Section 10. • Improved Per Protocol analysis set definition in Section 14.3 • Observed case data analysis without missing data imputation was clarified as the primary approach to handle missing data in Section 14.9. • Justification for margin of non-inferiority was added in Section 14.2 • Sensitivity analysis conducted on per-protocol (PP) population added on Section 14.5	For better clarity and completeness (Sections 5.2 and 5.3) Improved clarity (Section 10) For completeness (Section 14.3) Editorial correction (Section 14.9) For completeness (Section 14.2) To assess the robustness of results for the primary and secondary endpoint analysis (Section 14.5)	25 April 2023

SYNOPSIS

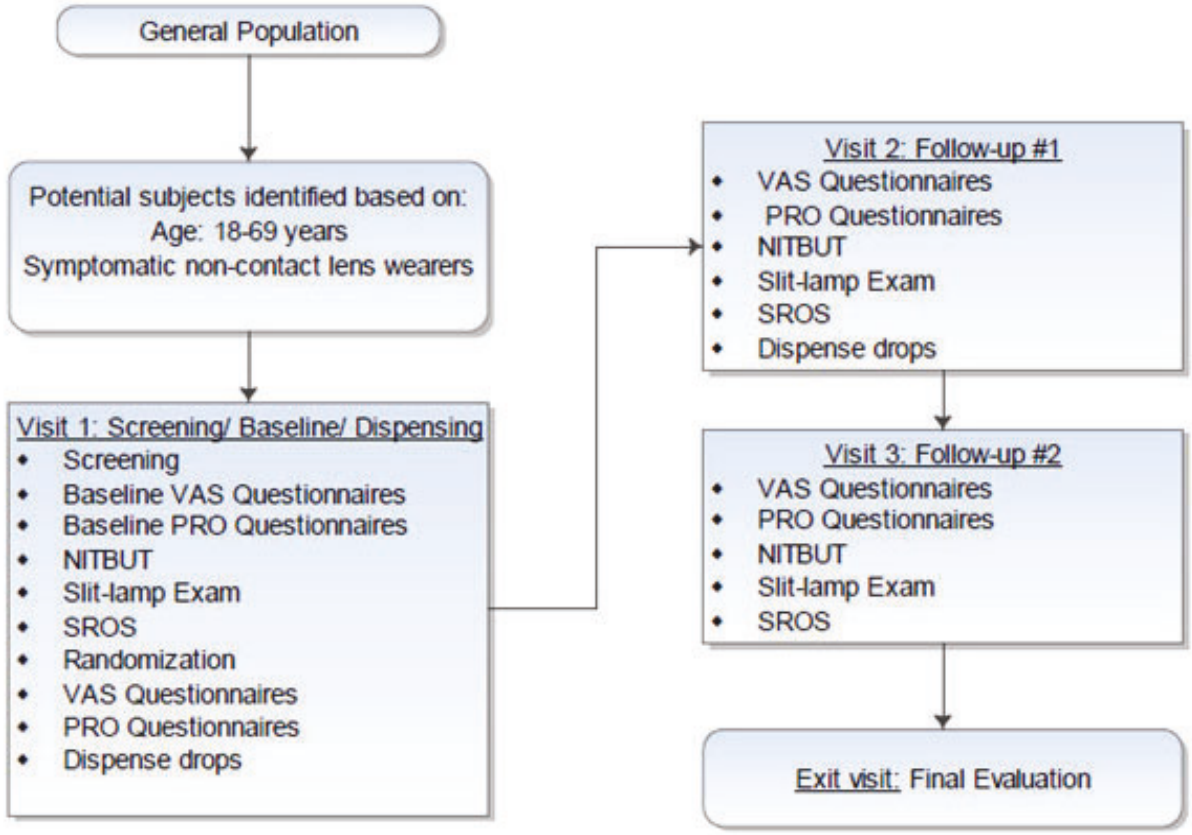
Protocol Title	Clinical Evaluation of a Multidose Preservative-free Lubricating Eye Drops Contained in Novelia® Eye Dropper in Non-Contact Lens Wearing Patients
Sponsor	JJVC, 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Clinical trial phase: Confirmatory Design control phase: Development phase 2
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)	Investigational Products: Investigational Eye Drops [redacted] in a Novelia® eyedropper (Test) Approved Products: Blink® Tears eye Drops (Control)
Treatment Doses	Dosage: Instill 1-2 drops OU at least 3-4 times a day or as needed (Not exceeding up to 6 times a day)
Objectives	The objective of this study is to evaluate the safety and the efficacy of an Investigational lubricating eye drops (Test) contained in a Novelia® eyedropper by comparison with Blink® Tears eye drops (Control). This study is being conducted to support product registration in the European Union.
Stuy Endpoints	**Primary endpoint(s):** • Change in overall ocular comfort from baseline at 30-Day follow-up using VAS **Secondary endpoint(s):** • Change in overall quality of vision from baseline at 30-Day follow-up collected using VAS **Other Observations** • Corneal staining Grade 2 or higher using FDA scale • Subject's reported ocular symptoms (yes/no) • 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. **Separate endpoint(s)** • Change in overall ocular comfort from baseline at 14-Day follow-up using VAS • Change in overall quality of vision from baseline at 14-Day follow-up using VAS • PRO Questionnaires

Study Design	This is a 30-Day, multi-site, single-masked, bilateral, active-controlled, 2-Arm parallel group study. Subjects are scheduled for 3 study visits (screening/baseline, 14-Day and 30-Day follow-up visits) over a period of one month.
Sample Size	Approximately 116 subjects (~58 per arm) will be enrolled and approximately 104 subjects (52 per arm) are targeted to complete the study.
Study Duration	The study will last approximately 4 months and including the 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 history of the use of artificial tears in the last 3 months.
Eligibility Criteria - Inclusion	Potential subjects must satisfy all of the following criteria to be enrolled in the study: Inclusion Criteria following Screening The subject must: 1. Read, understand, and sign the STATEMENT OF INFORMED CONSENT and receive a fully executed copy of the form. 2. Appear able and willing to adhere to the instructions set forth in this clinical protocol. 3. Be between 18 and 69 (inclusive) years of age at the time of screening. 4. Possess a wearable pair of spectacles that provide correction for distance vision and bring them to every visit (only if applicable- to the investigator's discretion). 5. Self-reported symptoms of ocular dryness and/or the use of artificial tears in the last 3 months. 6. Subjects must be non-contact lens wearers. Inclusion Criteria at Baseline Evaluation 7. Subjects must achieve visual acuity of 20/30 or better in each eye, either unaided or best corrected.

Eligibility Criteria - Exclusion	Potential subjects who meet any of the following criteria will be excluded from participating in the study: Exclusion Criteria following Screening The subject must not: 1. Be currently pregnant or lactating. 2. Be diabetic. 3. Be currently using any ocular medications or have any ocular infection of any type which may interfere with the clinical trial (at the investigator's discretion). 4. By self-report, have any ocular or systemic disease, allergies, infection, or use of medication that might contraindicate or interfere with the clinical trial, or otherwise compromise study endpoints, including infectious disease (e.g., hepatitis, tuberculosis), contagious immunosuppressive disease (e.g., Human Immunodeficiency Virus [HIV]), autoimmune disease (e.g., rheumatoid arthritis, Sjögren's syndrome), or history of serious mental illness or seizures. See section 9.1 for additional details regarding excluded systemic medications. 5. Have habitually worn rigid gas permeable (RGP) lenses, orthokeratology lenses, or hybrid lenses (e.g., SynergEyes, SoftPerm) within the past 3 months and soft contact lenses in the past 1 month. 6. Have participated in any pharmaceutical or medical device related clinical trial within 30 days prior to study enrollment. 7. Be an employee (e.g., Investigator, Coordinator, Technician) or immediate family member of an employee (including partner, child, parent, grandparent, grandchild or sibling of the employee or their spouse) of the clinical site. 8. Be a current habitual user of prescription medication to treat dry eye and ocular discomfort, ocular steroids, or any medication (Rx or OTC) that would interfere with the clinical study, except for artificial tears (at the discretion of the investigator). 9. Have any known allergy or sensitivity to ingredients that the investigational product may contain (e.g., Sodium Chlorite, Boric Acid, Sodium Borate Decahydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Polyethylene Glycol 400, Sodium Hyaluronate and Purified Water). Exclusion Criteria at Baseline Evaluation The subject must not: 10. Have clinically significant (grade 3 or higher on the FDA grading scale) slit lamp findings (e.g., corneal

	edema, neovascularization or staining, tarsal abnormalities, or bulbar injection) or other corneal or ocular disease or abnormalities that contraindicate participation or may otherwise compromise study endpoints (including entropion, ectropion, chalazia, recurrent styes, glaucoma, history of recurrent corneal erosions, aphakia, moderate or above corneal distortion, herpetic keratitis). 11. Have a history of strabismus or amblyopia. 12. Have had or have planned (within the study period) any ocular or intraocular surgery (e.g., radial keratotomy, PRK, LASIK, iridotomy, cataract removal, retinal laser photocoagulation, etc.). 13. Have any significant corneal distortion due to previous contact lens wear, surgery, or pathology (At the discretion of the investigator).
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 a Serious Adverse Event (SAE) for which a causal relationship to a test article cannot be ruled out, will result in stopping further dispensing investigational product. In the event of a 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), Fluorescein (Akorn, Inc.) or another 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, ACRONYMS AND DEFINITIONS OF TERMS

Add	Near addition; the additional power required for near vision correction
ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
BCVA	Best Corrected Visual Acuity
BSCVA	Best Spectacle Corrected Visual Acuity
CFR	Code of Federal Regulations
COAS	Complete Ophthalmic Analysis System
COM	Clinical Operations Manager
COVID-19	Coronavirus Disease 2019
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	The 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
JJVC	Johnson & Johnson Vision Care, Inc.
LC	Limbus Center
LogMAR	Logarithm of Minimal Angle of Resolution
MedDRA©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NAVQ	Near Activity Visual Questionnaire
NIH	National Institutes of Health
NIBUT	Non-Invasive Tear Break-Up Time
OD	Right Eye
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
OS	Left Eye
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
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SROS	Subject Reported Ocular Symptoms
VA	Visual Acuity

1. INTRODUCTION AND BACKGROUND

It is estimated that Dry Eye Diseases (DED) affect approximately 16 million patients over 18 years of age in the United States[5]. Topical artificial tears or tear supplements are often used to treat the symptoms of dryness and discomfort associated with the condition. Toxic effects of preservatives used in topical ocular formulations have been documented to induce conjunctival inflammation and tear-film instability in human and animal studies, highlighting the need for preservative-free options in topical preparations[6]. Given the potential of additional benefit of preservative-free topical tear supplements, JJV CEH has already introduced Blink® Tears Preservative Free lubricating eye drops in single dose vials. However, JJV CEH currently does not offer preservative-free topical tear supplements in a multidose dropper.

This study will investigate a new formulation of Investigational Lubricating eye drops [redacted] in a Novelia® eyedropper, along with the marketed Blink® Tears (Johnson & Johnson Surgical Vision, Santa Ana, CA) as a control in up to 8 clinical sites in the US.

Figure 2: The mechanism for dispensing drops in the Novelia® system

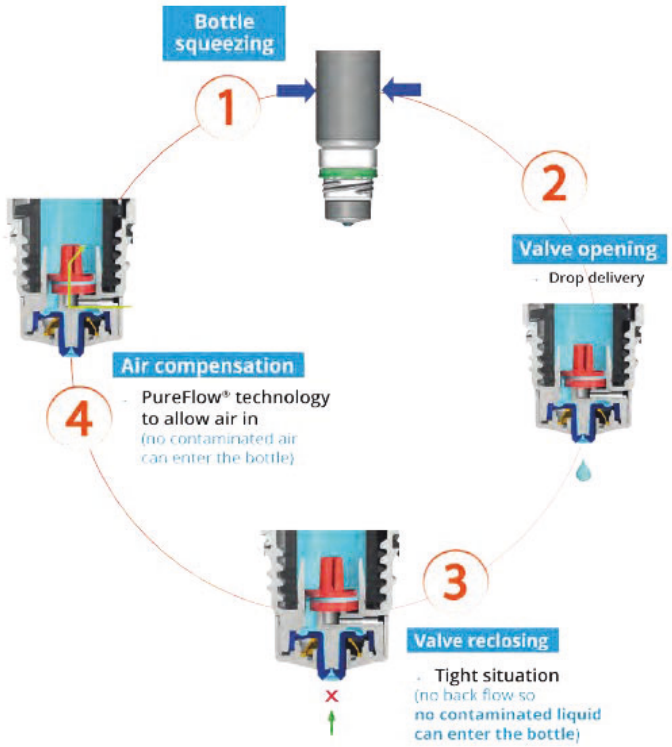


Figure 2 above shows the mechanism of drug delivery system utilized by in a Novelia® (Nemera Inc, France) eyedropper where the squeezing action of the bottle/eyedropper opens a valve which facilitates the dispensing of a single drop. The intricate system of valves closes immediately which stops the potential backflow of the drop which comes into contact with air/external environment, hence maintaining sterility of the formulations contained in the bottle.

1.1. Name and Descriptions of Investigational Products

The products which will be used in this clinical study is listed below:

- Investigational Eye Drops [redacted] in a Novelia® eyedropper (Test)

- Approved Products: Blink® Tears eye Drops (Control)

Blink® Tears is a marketed product with preservatives while the investigational lubricating eye drops do not contain any preservatives and are maintained sterile in a multi-dose Novelia® eyedropper.

1.2. Intended Use of Investigational Products

The investigational eye drops are developed as preservative-free lubricating eye drops, and the other product, proposed control drop 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 1-2 drops in both eyes at least 3-4 times a day or as needed (Up to 6 times a day) for 30 days.

The intended use of the study artificial tears is treatment of subjects with symptoms of ocular dryness. The indications for the investigational eyedrops are consistent with 21 CFR Part 349.60 pertaining to the demulcent eyedrops as per the FDA OTC monograph. The following are the indications:

- For the temporary relief of burning and irritation due to dryness of the eye.
- For the temporary relief of discomfort due to minor irritation of the eye or to exposure to wind or sun.
- For use as a protectant against further irritation or to relieve dryness of eye.
- For use as a lubricant to prevent further irritation or relieve dryness of the eye.

1.3. Summary of Findings from Nonclinical Studies

All previous pre-clinical findings were deemed satisfactory prior to proceeding with clinical trials on humans. For the most comprehensive nonclinical information regarding the investigational eye drops in a Novelia® eyedropper, refer to the latest version of 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, photosensitivity, 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 in the further development and design of new artificial tears.

For the most comprehensive clinical information regarding the control eyedrops refer to the package insert (Appendix C).

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

Refer to the Investigator's Brochure and package insert (Appendix C) for additional information.

2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

2.1. Objectives

The objective of this study is to evaluate the safety and the efficacy of an Investigational lubricating eye drops (Test) by comparison with Blink® Tears eye drops (Control).

This study is being conducted to support product registration in the European Union.

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, 14-Day and 30-Day follow-up using a Visual Analogue Scale (VAS) with continuous scale from 0 (extremely uncomfortable) to 100 (extremely comfortable)[7].

Secondary endpoint:
The secondary endpoint in this study is change in overall quality of vision score from baseline at 30-Day follow-up. Change in quality of vision from baseline will be assessed using Visual Analogue Scale (VAS) with continuous scale from 0 (extremely uncomfortable) to 100 (extremely comfortable) at 30-Day follow-up[7].

Other Exploratory Endpoints:
- Corneal Staining
- Subject's reported ocular symptoms
- 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.
- Change in overall quality of vision from baseline at 14-Day follow-up using VAS
- Change in overall ocular comfort from baseline at 14-Day follow-up using VAS
- PRO and MRD analysis

2.3. Hypotheses

Primary Hypothesis:
- 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 Hypothesis:

- The Test eye drops will be non-inferior to the Control eye drop with respect to change in overall quality of vision on a VAS scale from baseline at 30-Day follow-up. A non-inferiority margin of -20 point change in quality of vision 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 8 sites in the US.

3.2. Inclusion Criteria

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

Inclusion Criteria following Screening
The subject must:

1. Read, understand, and sign the STATEMENT OF INFORMED CONSENT and receive a fully executed copy of the form.
2. Appear able and willing to adhere to the instructions set forth in this clinical protocol.
3. Be between 18 and 69 (inclusive) years of age at the time of screening.
4. Possess a wearable pair of spectacles that provide correction for distance vision and bring them to every visit (only if applicable- to the investigator's discretion).
5. Self-reported symptoms of ocular dryness and/or the use of artificial tears in the last 3 months.
6. Subjects must be non-contact lens wearers.

Inclusion Criteria at Baseline Evaluation

7. The monocular, distance visual acuity must be *20/30* or better in each eye, either unaided or best corrected.

3.3. Exclusion Criteria

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

Exclusion Criteria following Screening
The subject must not:

1. Be currently pregnant or lactating.
2. Be diabetic.
3. Be currently using any ocular medications or have any ocular infection of any type which may interfere with the clinical trial (at the investigator's discretion).
4. By self-report, have any ocular or systemic disease, allergies, infection, or use of medication that might contraindicate or interfere with the clinical trial, or otherwise compromise study endpoints, including infectious disease (e.g., hepatitis, tuberculosis), contagious immunosuppressive disease (e.g., Human Immunodeficiency Virus [HIV]), autoimmune disease (e.g., rheumatoid arthritis, Sjögren's syndrome), or history of serious mental illness or seizures. See section 9.1 for additional details regarding excluded systemic medications.
5. Have habitually worn rigid gas permeable (RGP) lenses, orthokeratology lenses, or hybrid lenses (e.g., SynergEyes, SoftPerm) within the past 3 months or soft contact lenses in the past 1 month.

6. Have participated in any pharmaceutical or medical device related clinical trial within 30 days prior to study enrollment.
7. Be an employee (e.g., Investigator, Coordinator, Technician) or immediate family member of an employee (including partner, child, parent, grandparent, grandchild or sibling of the employee or their spouse) of the clinical site.
8. Be a current habitual user of prescription medication to treat dry eye and ocular discomfort, ocular steroids, or any medication (RX or OTC), except for artificial tears that would interfere with the clinical study (at the discretion of the investigator).
9. Have any known allergy or sensitivity to ingredients that the investigational product may contain (e.g., Sodium Chlorite, Boric Acid, Sodium Borate Decahydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Dihydrate, Magnesium Chloride Hexahydrate, Polyethylene Glycol 400, Sodium Hyaluronate and Purified Water).

Exclusion Criteria at Baseline Evaluation
The subject must not:

10. Have clinically significant (grade 3 or higher on the FDA grading scale) slit lamp findings (e.g., corneal edema, neovascularization or staining, tarsal abnormalities, or bulbar injection) or other corneal or ocular disease or abnormalities that contraindicate participation or may otherwise compromise study endpoints (including entropion, ectropion, chalazia, recurrent styes, glaucoma, history of recurrent corneal erosions, aphakia, moderate or above corneal distortion, herpetic keratitis).
11. Have a history of strabismus or amblyopia.
12. Have had or have planned (within the study period) any ocular or intraocular surgery (e.g., radial keratotomy, PRK, LASIK, iridotomy, cataract removal, retinal laser photocoagulation, etc.).
13. Have any significant corneal distortion due to previous contact lens wear, surgery, or pathology (At the discretion of the investigator).

3.4. Enrollment Strategy

Study subjects will be recruited from the Institution/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, single-masked, bilateral, controlled, 2-Arm parallel group, dispensing study. Approximately 116 subjects will be screened and randomly assigned to either Test or Control groups (58 subjects/arm). The goal is for a sample size of 104 (52 subjects/arm) after subjects who withdraw or are lost-to-follow-up. Subjects are scheduled for 3 study visits (screening/baseline, 14-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, or as needed (not exceeding 6 times a day) over a 14±2 day period. The follow-up evaluation (Visit 2) will occur 14±2 days after Visit 1.

At Visit 2, VAS, PRO and MRD 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, PRO and MRD questionnaires, SROS, NITBUT and slit lamp findings will be evaluated, and the subject will have a final evaluation before exiting from the study. All used and unused test articles will be collected from the subjects during the exit visit.

4.2. Study Design Rationale

Randomized, 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. Due to the difference in the shape of the eyedroppers, double masking will not be possible. However, the subjects will be masked from the identity of the lubricating eye drops. A parallel-group design allows for the comparison of the investigational eyedrops to existing marketed product which has received a CE mark in the EU. A 30-Day period is recommended for follow up in pivotal studies and is an appropriate review period based on studies which recognize the impact of cyclical changes to tear quality in female subjects[8].

4.3. Enrollment Target and Study Duration

A total of up to 116 subjects will be enrolled (informed consent signed) and randomized (58 per arm) from up to 8 clinical sites in the US. The goal is for 104 subjects (52 per arm) to complete. 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 (Investigational Lubricating Eye Drop in a Novelia® bottle)	Control (Marketed Blink® Tears)	Total
Randomization	58	58	116
Completion	54	54	104
Number of sites	8	8	8
Number of subjects per site	6-8	6-8	12-16

The study will last approximately 4 months and includes an approximately 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. Subjects who are discontinued prior to the final evaluation may be replaced at the discretion of the study sponsor. The investigation will end at the time that the study data is hard locked.

5. TEST ARTICLE ALLOCATION AND MASKING

5.1. Test Article Allocation

Subjects will be randomly assigned to a Test group, or a Control group based on a computer-generated randomization schedule prepared before the start of the study in a 1:1 order. Equal number of subjects will be randomized to the 2 treatment arms. The randomization will be stratified by investigational site and randomly permuted blocks 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). 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. 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

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 schedule 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 schedule.
3. Investigator or designee will pull the appropriate test articles from the study supply. All test articles that are opened, whether dispensed (placed on eye or dispensed outside the clinical site) or not, must be recorded on the Test Article Accountability Log in the "Dispensed" section.

5.2. Masking

Masking will be used to reduce potential bias. Due to the difference in shape of the marketed eye drops compared to the test eye drops, double masking is not possible. However, the subjects will be masked from the identity of the eye drops. 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. Investigators and clinical site personnel involved in the data collection will not be masked as to the identity of the investigational product.

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.

Subjects who have had their treatment assignment unmasked are expected to return for all remaining scheduled evaluations. Subjects who are discontinued will be replaced.

6. STUDY INTERVENTION

6.1. Identity of Test Articles

The following test articles will be used in this study:

Table 2: Test Articles

	Test	Control
Name	Investigational lubricating eye drop [redacted] in a Novelia® bottle	Blink® Tears
Manufacturer	Johnson and Johnson Surgical Vision	Johnson and Johnson Surgical Vision
Ingredients	Boric Acid, Sodium Borate Dehydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Hexahydrate, Polyethylene Glycol 400, Magnesium Chloride Hexahydrate, Sodium Hyaluronate, Purified water	Sodium Chlorite, Boric Acid, Sodium Borate Dehydrate, Sodium Chloride, Potassium Chloride, Calcium Chloride Hexahydrate, Polyethylene Glycol 400, Magnesium Chloride Hexahydrate, Sodium Hyaluronate, Purified water
Packaging form	Over-labeled	Over-labeled

With 116 subjects targeted to be enrolled in the study and each subjects receiving 2 units/bottles of eye-drops each; 232 units/bottles of Test or Control articles is estimated to be used in the study.

6.2. Ancillary Supplies/Products

The following solutions will be used in this study:

Table 3: Ancillary Supplies

	Solution	
Solution name/ Description	Sclerafil® Preservative Free Saline Solution (or other sponsor-approved product)	Fluorescein (or other sponsor-approved product)
Manufacturer	Bausch & Lomb	Akorn Inc.
Preservative	None	None
Other distinguishing items (dye, packaging, approval status, etc.)	N/A	D&C Yellow No. 8, 0.6 mg

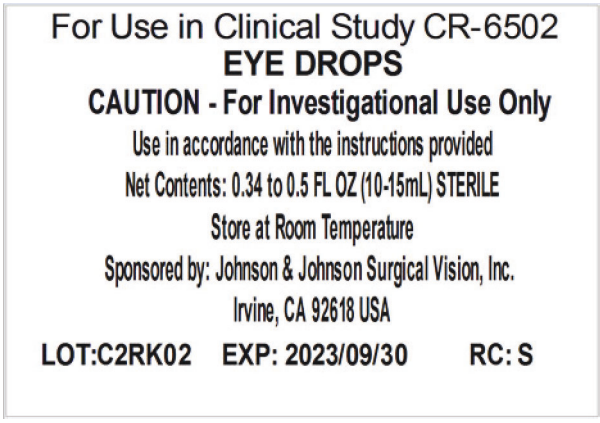
Sodium fluorescein dye will be used for biomicroscopy, as needed. Sterile, preservative free, saline may be used in this clinical study to rinse each eye.

6.3. Administration of Test Article

Test articles will be dispensed to subjects 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 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 of the eyedrops. The test articles will be in plastic bags as the secondary packaging form. The sample study label is shown below:



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 Event and/or a Product Quality Complaint must be retained pending directions from the sponsor for potential return to JJVC.

6.7. Accountability of Test Articles

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

Test articles must be kept in a locked storage cabinet, 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, to use out of the office, or issued for the subject to replace appropriately between visits.
2. What was returned to the Investigator unused, including expired or malfunctioning product.
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 JJVC.

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 4: Time and Events

Visit Information	Visit 1 Screening, Baseline, Dispense Drop	Visit 2 Follow-up #1	Visit 3 Follow-up #2
Time Point	Day 0	14+/- 2 days after V1	30 +/- 2 days after V1
Estimated Visit Duration	2.5 hours	1.0 hour	1.0 hour
Statement of Informed Consent	X		
Demographics	X		
Medical History/Concomitant Medications	X		
Adverse Event Review		X	X
Compliance		X	X
Habitual Artificial tear Usage	X		
Average drops applied for OD and OS	X	X	X
Maximum number of drops applied for OD and OS (If applicable)	X	X	X
Screening Inclusion/Exclusion Criteria	X		
Eligibility after Screening	X		
Entrance Distance Visual Acuity	X	X	X
SROS Questionnaire	X	X	X
VAS Questionnaire	X	X	X
PRO Questionnaire	X *(If applicable)*	X	X
Non-invasive Tear Break-up Time	X	X	X
Biomicroscopy	X	X	X
Eligibility after Baseline	X		
Randomization	X		
Drop Installation	X		
Drop Dispensing & Instructions	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 requested 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 before being enrolled into the study. The Principal Investigator or his/her 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 year of birth, age, gender, race, and ethnicity.	
1.3	Medical History and Concomitant Medications	Questions regarding the subject's 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. *If subject is deemed to be ineligible after screening, proceed to Final Evaluation and complete Subject Disposition. Refraction and Biomicroscopy forms are not required.*	

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 Subject Reported Ocular Symptoms	Subjects will respond to a verbal open- ended symptoms questionnaire.	[redacted]
1.8	Baseline VAS	The subject will respond to the VAS questionnaire using the Kiosk portal.	[redacted]
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 (NIBUT), OD and OS, with a Medmont or other topographer.	NIBUT work aid (Appendix D)
1.11	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings and determine eligibility.	[redacted]

Visit 1: Baseline			
Step	Procedure	Details	[redacted]
		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 saline may be instilled.	
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 installation	The investigator will break the seal and discard the first drop. 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	Subject Reported 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 using the Kiosk portal	[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, or as needed (up to 6 times a day) OU for 14 +/- 2 days.	
1.23	Review of Patient Instruction Guide	The investigator will review the patient instruction guide with the subject	

Visit 1: Dispensing			
Step	Procedure	Details	[redacted]
1.24	Dispense	The artificial tears will be dispensed for a 14 +/- 2 day dispensing period • Dispense one bottle of artificial tears • 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 14 +/- 2 days. • Subjects will be instructed to bring the dispensed bottle of artificial tears to the next visit. • Subjects will be instructed not to use other artificial tears during the dispensing period.	

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 as instructed.

Visit 2: Follow-up 1			
Step	Procedure	Details	[redacted]
2.1	Adverse Events and Concomitant Medications Review	Review the subject's concomitant medications and record any changes from the previous study visit. Record any adverse events or medical history changes from the previous study visit.	
2.2	Artificial Tear Compliance	Confirm the subject used the drops as instructed and record the average and maximum number of drops used in OD and OS per day.	
2.3	Collection of study drops	This bottle will be collected by the site 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 using the Kiosk portal.	[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 (NIBUT), OD and OS, with a Medmont or other topographer.	NIBUT work aid (Appendix D)
2.10	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings and determine eligibility. If the clearance of the fluorescein needs to be expedited, preservative-free saline may be instilled.	[redacted]
2.11	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (FDA grading scale) will be assessed using a more detailed scale for internal purposes only.	[redacted]
2.12	Exit Visual Acuity	Record the distance high contrast visual	[redacted]

Visit 2: Follow-up 1			
Step	Procedure	Details	[redacted]
		acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	
2.13	Continuance	For the subject to continue in the study, they must meet both of the following criteria: • Exit Visual acuity is 20/30 or better OD and OS • Subject willing to use the drop 3-4 times a day, or as needed (up to 6 times a day) OU until Visit 3.	
2.14	Dispense	• Dispense one bottle of artificial tears • 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 Visit 1. • Subjects will be instructed to bring the dispensed bottle of artificial tears to the next visit.	

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 as instructed.

Visit 3: Follow-up 2			
Step	Procedure	Details	[redacted]
3.1	Adverse Events and Concomitant Medications Review	Review the subject's concomitant medications and record any changes from the previous study visit. Record any adverse events or medical history changes from the previous study visit.	
3.2	Artificial Tear Compliance	Confirm the subject used the drops as instructed and record the average and maximum number of drops used in OD and OS per day.	
3.3	Collection of study drops	This bottle will be collected by the site and discarded.	
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 using the Kiosk portal.	[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]

Visit 3: Follow-up 2			
Step	Procedure	Details	[redacted]
3.9	Tear Break up Time	Record the tear film stability (NIBUT), OD and OS, with a Medmont or other topographer.	NIBUT work aid (Appendix D)
3.10	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings and determine eligibility. If the clearance of the fluorescein needs to be expedited, preservative-free saline may be instilled.	[redacted]
3.11	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (FDA grading scale) 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 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]
F.3	Exit Slit Lamp Biomicroscopy (for subjects that are discontinued early)	FDA Slit Lamp Classification Scale will be used to grade the findings. If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled. This step is not necessary if the subject was exited due to screen failure. **Note: This step is not necessary if the subject was exited due to screen failure, or if biomicroscopy was performed as part of the final follow-up visit procedures (i.e., immediately prior to the final evaluation).**	[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, as appropriate:

- Chief complaint prompting the visit. If the reason is an adverse event, the applicable eCRF for the adverse event must be completed and the subject record completed as appropriate.

- Date and time of the visit and all procedures completed at the unscheduled visit.
- Review of adverse events 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.

Unscheduled Visit			
Step	Procedure	Details	[redacted]
U.1	Reason for unscheduled visit	Indicate if the only reason for the visit is that the subject requires additional test eye drops. If the reason is other than resupply of previously dispensed eye drops, specify the reason for the visit.	
U.2	Chief Complaints (if applicable)	Record the subject's chief complaints for reasons for the unscheduled visit.	
U.3	Adverse Events and Concomitant Medications Review (if applicable)	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.4	Entrance Visual Acuity (if applicable)	Record the entrance distance visual acuity (OD, OS and OU) to the nearest letter.	[redacted]
U.5	Subjective Sphero-cylindrical Refraction (if applicable)	Perform bare-eye subjective spherocylindrical refraction with a phoropter (adopt the maximum plus to maximum visual acuity (MPMVA) approach and use the duo-chrome test for binocular balancing) and record the best corrected distance visual acuity to the nearest letter (OD, OS).	[redacted]
U.6	Slit Lamp Biomicroscopy (if applicable)	FDA Slit Lamp Classification Scale will be used to grade the findings. If the clearance of the fluorescein needs to be expedited, preservative-free saline may be instilled.	[redacted]
U.7	Dispensing (if applicable)	If the subject requires additional test eye drops to complete the study period and is eligible to do so, provide additional eye drops per the dispensing instructions given in the detailed study procedures.	
U.8	Exit Visual Acuity (if applicable)	Record the subject's exit distance visual acuity (OD, OS, and OU) to the nearest letter.	[redacted]

NOTE: If the only reason for the unscheduled visit is that the subject requires additional test articles, only the dispensing information needs to be recorded.

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
- Not have withdrawn/ discontinued from the study for any reason described in section 4.2.

8.2. Withdrawal/Discontinuation from the Study

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

- Subject withdrawal of consent.
- Subject not compliant to 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 necessitating discontinuation of study eyedrops
- 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 deemed incapable of dispensing the drops safely and effectively (Based on investigator's judgment.

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.
- Record the spherocylindrical refraction with best corrected distance visual acuity.
- Collect used test article(s) (used or 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.
- Make arrangements for subject care, if needed, due to their study participation

Additional subjects will be enrolled if a subject discontinues from the study prematurely (within the enrollment window specified by the sponsor).

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 Diseases or ocular discomfort, ocular steroids, or any medications (either prescription-only 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 medications for dry eye diseases and ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).

9.1. Systemic Medications

Certain systemic medications are known to have a higher likelihood to disrupt the tear film.

A summary of disallowed systemic medications is shown in Table 5: Systemic medications list. Subjects with a history of taking these medications will be allowed to enroll only if:

- The subject was taking the medication on a temporary basis and ceased taking that medication at least 4 weeks prior to signing the informed consent (this is considered sufficient time for the medication to have left the body prior to enrollment).

Subjects with a history of taking medications listed in Table 5 on a long-term, routine basis will not be allowed to participate in the study.

Table 5: Systemic medications list

Class of Drug	Common Indication(s)	Common Examples
Anticholinergics	Irritable bowel syndrome, Parkinson's disease, peptic ulcer, cystitis, nasal congestion, cold symptoms, overactive bladder, COPD	Bentyl, Spiriva, Atrovent, Hyosyne, Levsin, Symax Fastab, Symax SL, Homax SL, Cogentin, Transderm Scop, etc., …
Oral Phenothiazines	Antipsychotic disorders (schizophrenia, mania)	Compazine, Mellarill, Thorazine, Phenagran, etc.…
Oral Retinoids	Cystic acne	Isotretinoin
Corticosteroids	Arthritis, colitis, asthma, bronchitis, allergic or inflammatory conditions	Cortisone, Prednisone, Hydrocortisone, Medrol, Kenalog etc., …
Oral Tetracycline	Urinary Tract Infection, acne, chlamydia, gonorrhea	Sumcyin, Acitsite, Achromycin V, etc.

Examples of disallowed systemic antihistamines are given below. Subjects with a history of taking systemic antihistamines will be allowed to enroll only if:

- They have taken antihistamines continuously for at least 2 weeks with no residual symptoms as per investigator's discretion

Or:

They stopped taking the medication for at least 2 weeks prior to enrollment.

Table 6: Disallowed systemic antihistamines

Class of Drug	Common Indication(s)	Common Examples
Oral antihistamines	Allergic rhinitis, allergic dermatologic reaction, sinusitis, allergic conjunctivitis, nausea, motion sickness etc.	Hydroxyzine, Promethagan, Phenadoz, Vistaril, Claritin, Zyrtec, stepro, Astelin, Optivar, Allegra, Benadryl, etc.

10. DEVIATIONS FROM THE PROTOCOL

Investigator will notify study sponsor upon identification of a protocol deviation. 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 in order 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.

If the deviation potentially impacts the safety of patient or changes the technical integrity of the study, then it must be reported to IEC/IRB. This is a "Major Deviation". Deviations that contradict the information contained in the Informed Consent/Assent forms will be considered Major Deviations.

Minor deviations have no substantive effect on patient safety or technical integrity of the study. They are often logistical in nature.

Protocol waivers are prohibited.

Table 7 lists examples of deviations that will constitute major and minor protocol deviations for this study.

Table 7: Examples of major and minor protocol deviations

Deviation category	Major deviation	Minor deviation
Out-of-window visit	Visit attended more than 2 days out of visit window defined in study procedures.	Visit attended 2 or fewer days out of visit window defined in study procedures
Unanswered PRO questions	Unanswered (i.e. left blank) question related to the primary endpoint (VAS comfort at Day 30) and secondary endpoint (VAS Vision at Day 30), respectively.	Unanswered (i.e. left blank) question related to the primary endpoint (VAS comfort at any time) or secondary endpoint (VAS Vision at any time), respectively; and/or any other unanswered PRO questions not related to primary/secondary endpoint (i.e., left blank) at any time.
Insufficient use of study eye drops	Subject does not use study drops at least 3 times per day on at least 5 days of the study period.	Subject does not use the study eye drops during the day of the follow up visit.

11. STUDY TERMINATION

If more than 2 subjects in the investigational lubricating eyedrop group develop serious expected (e.g., definite, or probable MK) or unexpected eyedrop related adverse events, the study will be suspended. Upon review and consultation with IRB, DMC, and JJVC Safety Management Team, the study may be terminated.

The occurrence of one or more unexpected Serious Adverse Drug Reactions (ADR), 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 an unexpected ADR 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.

JJVC 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 JJVC, it is determined that it would be unwise to continue at the clinical site.

JJVC (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 product quality complaints:

- 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 (i.e. tears, rips, etc.), 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 eyedrop was used.
- Any related AE number if applicable.
- Detailed complaint description (scheduled/unscheduled visit, time of eyedrop usage, 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 apply 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 in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product"

NOTE: This definition includes events related to the investigational medical device or the comparator, and to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices/drugs. [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.

NOTE: 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 adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject that resulted in any of the following:
- Life-threatening illness or injury
- Permanent or persistent impairment of a body structure or a body function
- Hospitalization or prolongation of patient hospitalization
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease
- Foetal distress, foetal death or a congenital physical or mental impairment of birth defect.

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 – are defined as events that are symptomatic and warrant discontinuation (temporary or permanent) of the test articles (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)
- 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 eyedrop discontinuation > 2 weeks

Non-Significant Adverse Events – are defined as those events that are usually asymptomatic and usually do not warrant discontinuation of tear supplement use but may cause further symptoms. However, the Investigator may choose to prescribe treatment as a precautionary measure.

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

- Non-significant Infiltrative Event (NSIE)

- Papillary Conjunctivitis
- Superficial Punctate Keratitis (SPK)
- Conjunctivitis: Bacterial, Viral, Allergic
- Blepharitis
- Meibomianitis
- Contact Dermatitis
- Localized Allergic Reactions or infections
- Any corneal event not explicitly defined as serious or significant adverse event, which necessitates temporary eyedrop discontinuation < 2 weeks

Adverse Drug Reaction (ADR) – An ADR is referred to all "noxious and unintended responses to a drug product related to any dose where a causal relationship between a medical product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."[2]

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, or 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, or severe - see definition in section 13.2.2).
- Outcome – not recovered or not resolved, recovering, or resolving, recovered, or resolved with sequelae, recovered or resolved, death related to adverse event, or unknown.
- Actions Taken – none, temporarily discontinued, permanently discontinued, or 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) begin 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 and 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 (where appropriate), 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, if the AE is related to the visual system.

Upon discovery of an AE that is deemed 'possibly related' or 'related' to the test article or study procedures (whether related to the visual system or not), an AE review form [redacted] must be completed. Additional dated and initialed entries should be made at follow-up evaluations. Separate forms must be completed for each eye if the AE is bilateral.

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 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 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.

Non-Serious Adverse Events
All non-serious adverse events, including non-serious adverse drug reactions, 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 to the written guidelines, including reporting timelines.

13.5. Event of Special Interest

None

13.6. Reporting of Pregnancy

Subjects reporting pregnancy (by self-report) during 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. Pregnant participants are not discontinued from artificial tear solution related studies for safety concerns, but due to general concerns relating to pregnancy and solution 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.

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. Unscheduled visits will be summarized separately and will be excluded from any efficacy analyses. However, unscheduled visits will be included in any analysis that may be conducted on safety endpoints.

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

This study was designed and powered to test for non-inferiority of the Test relative to the Control eye drops with respect to the overall ocular comfort score using Visual Analog Scale for Ocular Comfort (VAS), with a minimum power of 90% and two-sided Type I error rate of 0.05. A non-inferiority margin of -20 will be used to test the hypothesis. If the Test eye drops perform on average worse by more than 20 points on the VAS may be considered clinically unacceptable.

Historical data from a previous study, [redacted], was utilized in assessing scenarios for power analysis of the VAS. Summary statistics from the historical study [redacted] are presented in Table 8. The historical VAS, for the difference of 30 days follow-up from baseline scores, shows a slight left skew, indicating there is a possibility of a non-normally distributed result in this study. Hence, the sample size calculations were conducted using (i) two-sided, parametric two-sample t-test for normally distributed data, and (ii) non-parametric Wilcoxon Rank Sum test for non-normal data in PASS software Version 21.0.6 (2021) (NCSS LLC, Kaysville UT)[11].

Table 8: Summaries for Historical Overall Comfort Score Change from Baseline at 30-Day Follow-up using Visual Analog Scale (VAS) Questionnaire - Intent-To-Treat Population

Group	Number Analyzed	Mean Difference	Standard Deviation	Minimum	Median	Maximum
Blink® Tears	80	12.5	25.74	-69	13.0	62.0
Investigational Lipid Drop	75	20.3	23.24	-21	18.0	78.0

The common standard deviation considered was based on results from study [redacted], in which the estimated standard deviation of change in overall ocular comfort score from baseline at 30-day in the control group was estimated to be 25.74. In addition to the historical standard deviation value (25), the standard deviation was assumed to be 30 and 35, respectively, given the possibility of more variation being observed in the Test group. The estimated effect size (difference in change from baseline at 30-day follow-up between Test and Control) was assumed to be 0 as a more conservative estimate compared to the effect size observed in [redacted]

Sample Size Calculation using Parametric Method

Table 9 displays the sample size estimates for the primary endpoint using a two-sample *t*-test for non-inferiority, for different scenarios of standard deviations and dropout rates.

Table 9: Sample size calculations using two-sample t-test for non-inferiority

Standard deviation	Sample size per arm	Total sample size	Sample size per arm including a 5% dropout rate	Total sample size including 5% dropout rate	Sample size per arm including a 10% dropout rate	Total sample size including 10% dropout rate
25	34	68	36	72	38	76
30	49	98	52	104	55	110
35	66	132	70	140	74	148

Note: Sample size relating to 90% power, Type I Error rate of 0.05, assumed effect size of 0, non-inferiority margin of -20.

Sample Size Calculation using Non-Parametric Method

Table 10 displays the sample size estimates for the primary endpoint using Wilcoxon Rank Sum test for non-inferiority, for different scenarios of standard deviations and dropout rates.

Table 10: Sample size calculations using Wilcoxon Rank Sum test for non-inferiority

Standard deviation	Sample size per arm	Total sample size	Sample size per arm including a 5% dropout rate	Total sample size including 5% dropout rate	Sample size per arm including a 10% dropout rate	Total sample size including 10% dropout rate
25	36	72	38	76	40	80
30	52	104	55	110	58	**116**
35	70	140	74	148	78	156

Note: Sample size relating to 90% power, Type I Error rate of 0.025, assumed effect size of 0, non-inferiority margin of -20.

The recommended sample size is approximately 116 subjects which is determined to be sufficient to meet both normal and non-normally distributed options.

14.3. Analysis Populations

Safety Population:
All subjects who are administered any test article excluding subjects who drop out prior to administering any test article. At least one observation should be recorded.

Per-Protocol Population:
All subjects who successfully complete all visits and do not substantially deviate from the protocol (i.e. have major protocol deviations) as determined by the trial cohort review committee prior to database hard lock. Justification for the exclusion of subjects with major protocol deviations from the per-protocol population set will be documented in a memo to file.

Intent-to-Treat (ITT) Population:
All randomized subjects regardless of actual treatment and subsequent withdrawal from the study or deviation from the protocol. At least one observation should be recorded.

14.4. Level of Statistical Significance

All planned analysis for this study 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

All primary and secondary analyses will be conducted on intend-to-treat (ITT) population. Because the hypotheses are testing the non-inferiority of the Test related to the Control, a sensitivity analysis for the primary and secondary hypotheses will be performed on the per-protocol (PP) population to assess the robustness the results.

Ocular Comfort (VAS) Score:
Ocular Comfort scores are recorded using Visual Analogue Scale of 0 to 100.

Primary Hypotheses for Plan A or Plan B:
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 in mean change from baseline at 30-Day follow-up between treatment group and control group (Test minus Control).

The Ocular Comfort Scores will be analyzed for normality using the Shapiro-Wilk test. If the data is normally distributed, then *Primary Analysis Plan A* will be implemented. Otherwise, *Primary Analysis Plan B* will be implemented.

Primary Analysis Plan A (Assuming Normality)

The overall change of ocular comfort score from baseline at 30-Day follow-up will be analyzed using a linear mixed model. The subjects are the level one units, and the investigational sites are the level two units. The model will include treatment group (Test, Control) as a fixed effect, and investigational site as a random effect. Age and gender will be included in the model as covariates. The log-likelihood ratio test may be used to assess the homogeneity of the variances with respect to treatment and sites. The Kenward and Roger[12] method will be used to calculate the denominator degree of freedom.

The model for each hypothesis is:
Let y_{ij} denote the change in VAS ocular comfort score from baseline at 30-Day follow-up for the j^{th} subject from the i^{th} site $(j = 1, \dots, n; i = 1, 2, \dots, 8)$. The linear mixed model will be constructed as follows:

$$y_{ij} = \beta_0 + \beta_1 \cdot BASE_{ij} + \beta_2 \cdot TRT_{ij} + \beta_3 \cdot Age_{ij} + \beta_4 \cdot Gender_{ij} + \delta_i + \epsilon_{ij},$$

where

- β_0 = Intercept
- $BASE_{ij}$ = VAS ocular comfort score at baseline for the j^{th} subject in the i^{th} investigational site
- TRT_{ij} = treatment assigned to the j^{th} subject in the i^{th} investigational site (Test vs Control eye drop group)
- β_2 = the treatment effect of interest
- δ_i = a random effect (subject-specific intercept) term for the i^{th} site
- ϵ_{ij} = a random error associated with the j^{th} subject in the i^{th} investigational site.

Assume that δ_i and ϵ_{ij} are independent and identically distributed such that $\delta_i \sim N(0, \sigma^2_{site})$; $\epsilon_{ij} \sim N(0, \sigma^2)$, and are independent of each other.

The non-inferiority test will be based on the least square mean change difference and corresponding 95% confidence interval from the final model. Non-inferiority will be concluded if the lower limit of the 95% confidence interval is above non-inferiority margin of -20.

Primary Analysis Plan B (Assuming-non-normal distribution)

The difference of VAS Ocular comfort scores between treatment group and control group in mean change from baseline at 30-Day follow-up (Test minus Control) and two-sided 95% confidence interval

will be computed using a bootstrap methodology[13]. A total of 4000 bootstrap iterations will be used following the suggestions of Samuelson and Petrick[14]. Bias-adjusted 95% confidence interval will also be calculated. The assessment of the impact of the autocorrelation for between subjects repeated measurements, is defined by the difference between the observed statistic compared to the bootstrapped population mean (bias = observed minus bootstrapped population mean). This approach was recommended for all estimations of statistical inference since it accommodates correlated data. The bootstrap analysis will be performed using SAS MACRO procedures as discussed by Davison, AC and Hinkley, DV[12].

The non-inferiority test will be based on mean change difference and corresponding 95% confidence interval using the 2.5th percentile and 97.5th percentile from the bootstrapping 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 or equal to -20, the null hypothesis will be rejected, and the Test will be considered non-inferior to Control.

14.6. Secondary Analysis

Change in Overall Quality of Vision from Baseline at 30-Day Follow-Up Using VAS Scores
The overall change of quality of vision from baseline at 30-Day follow-up will be analyzed with the same hypotheses and models as primary analyses. If the Shapiro-Wilks test result is significant, then *Primary Analysis Plan B* will be adapted for overall change of quality of vision at 30-Day follow-up. Otherwise, *Primary Analysis Plan A* will be adapted for this secondary analysis.

Hypothesis Testing:
The two separate 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 group in mean change from baseline at 30-Day follow-up (Test minus Control).

14.7. Other Exploratory Analysis

Exploratory analyses will only be conducted if all primary and secondary hypotheses are met. If conducted, exploratory analysis will be analyzed for the Safety population. The exploratory analyses will be analyzed as follows:

Change in Overall Ocular Comfort from Baseline at 14-Day Follow-Up Using VAS Scores
The overall change in ocular comfort from baseline at 14-Day follow-up will be analyzed as described in primary analyses (section 14.5).

Change in Overall Quality of Vision from Baseline at 14-Day Follow-Up Using VAS Scores
The overall change in ocular comfort from baseline at 14-Day follow-up will be analyzed as described in secondary analyses (section 14.5).

Corneal Staining (Grade 2 or higher) Using FDA Scale
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 monitored by surveillance tabulation by

treatment group. If the rates between groups are significantly different from each other, then further analyses will be performed.

Subject's reported ocular symptoms
Subjects are asked to report if they experienced any ocular symptoms at Baseline and during each follow-up. If the number of reported ocular symptoms exceeds 5% total population, further analyses will be done to investigate the correlation of ocular symptoms to the Test drops.

14.8. Interim Analysis

No interim analysis is planned in this study.

14.9. Procedure for Handling Missing Data and Drop-Outs

All analyses will be performed on observed case data. Missing values will not be imputed. The count of missing values will be included in the summary tables and listings. In the event that more than 10% (10 subjects) have missing data, a sensitivity analysis will be conducted for the primary and secondary endpoints using multiple imputation method. Full details regarding methods for the imputations will be outlined in SAP.

14.10. Procedure for Reporting Deviations from Statistical Plan

The analysis will be conducted according to that specified in 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 the Clario EDC system. 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 JJVC database manager and sent to JJVC for analysis. External data sources for this study are not applicable

The clinical data will be recorded on dedicated eCRFs specifically designed to match the study procedures for each visit. Only specifically delegated staff can enter data on a CRF. 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 ISO14155:2020. [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.

15.3. Trial Registration on ClinicalTrials.gov

This study will be registered on ClinicalTrials.gov by the Sponsor.

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, JJVC 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 JJVC. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that JJVC 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 JJVC 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 JJVC and for inspection by local and regulatory authorities.

16.4. Data Monitoring Committee (DMC)

Not applicable

17. CLINICAL 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 versions, 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. Subjects will only be enrolled if the subject is fully able to understand the risks, benefits, and potential adverse events of the study and provide their consent voluntarily

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, according to ISO 14155:2020,[1] ICH-GCP E6 (R2)[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[2] and that the clinical study data are credible. The Investigator must maintain clinical study files in accordance with 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.
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information).
- 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, 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 revisions
- 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 revisions
- 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 revisions that increase subject risk, the revisions 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 or their representative, 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,[2] and ISO 14155:2020 guidelines[1], 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) in the United States[15] 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 ISO 14155:2020[1], guidelines, 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 ISO 14155:2020,[1] 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 JJVC.

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 JJVC management representative prior to study initiation.

JJVC 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.

JJVC 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

There is currently no plan to publish this outcome of this investigation.

22. REFERENCES

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2. International Council for Harmonisation Good Clinical Practice E6(R2) (ICH-GCP). Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
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. Clayton JA. 2018. *New England Journal of Medicine*. 378(23):2212-2223.
6. 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.
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10. SAS/STAT® 15.1 User's Guide. Cary, NC: SAS Institute Inc.; 2018.
11. PASS: Power Analysis and Sample Size Software. Kaysville, Utah, USA.: NCSS LLC; 2021.
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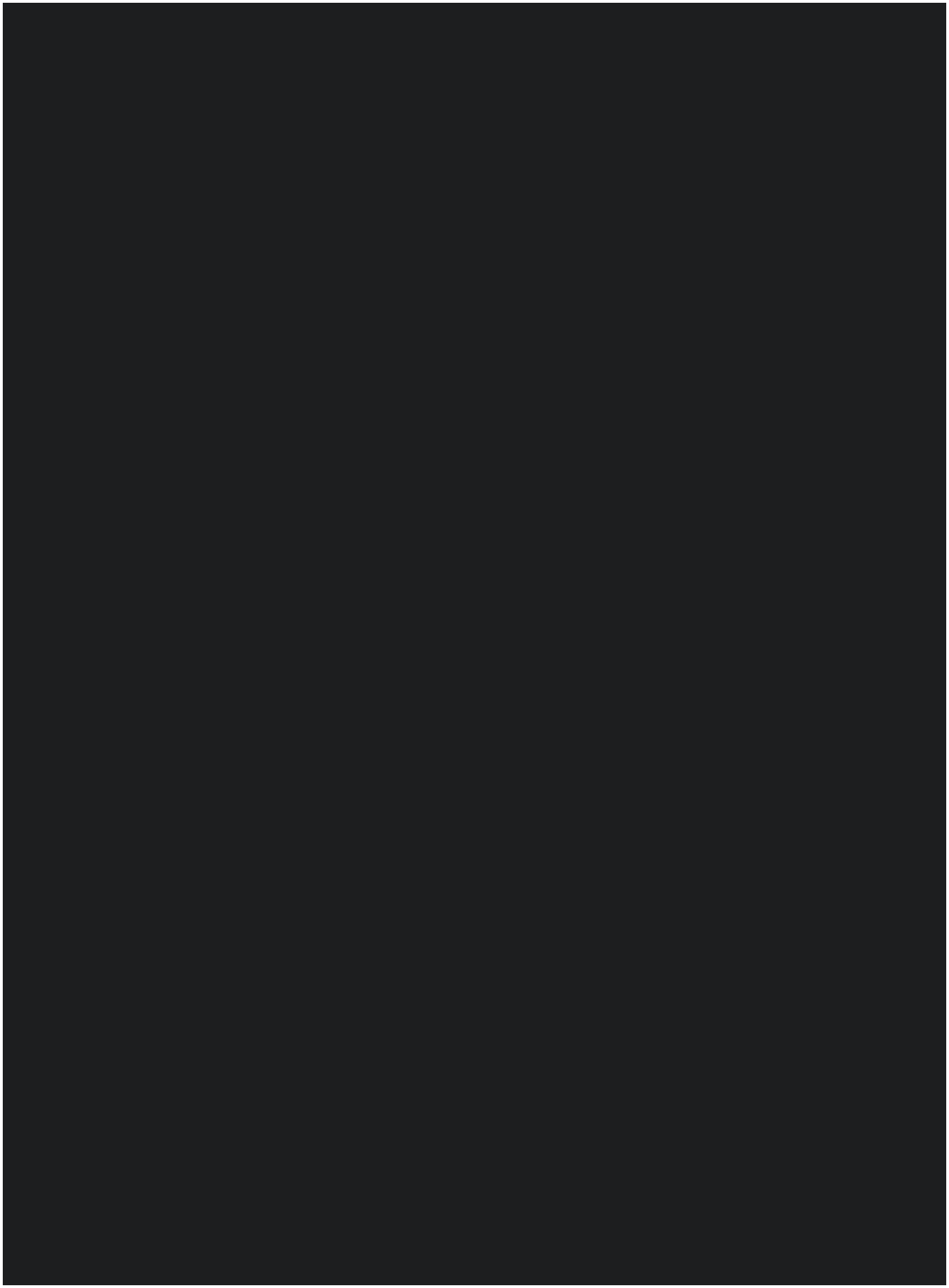
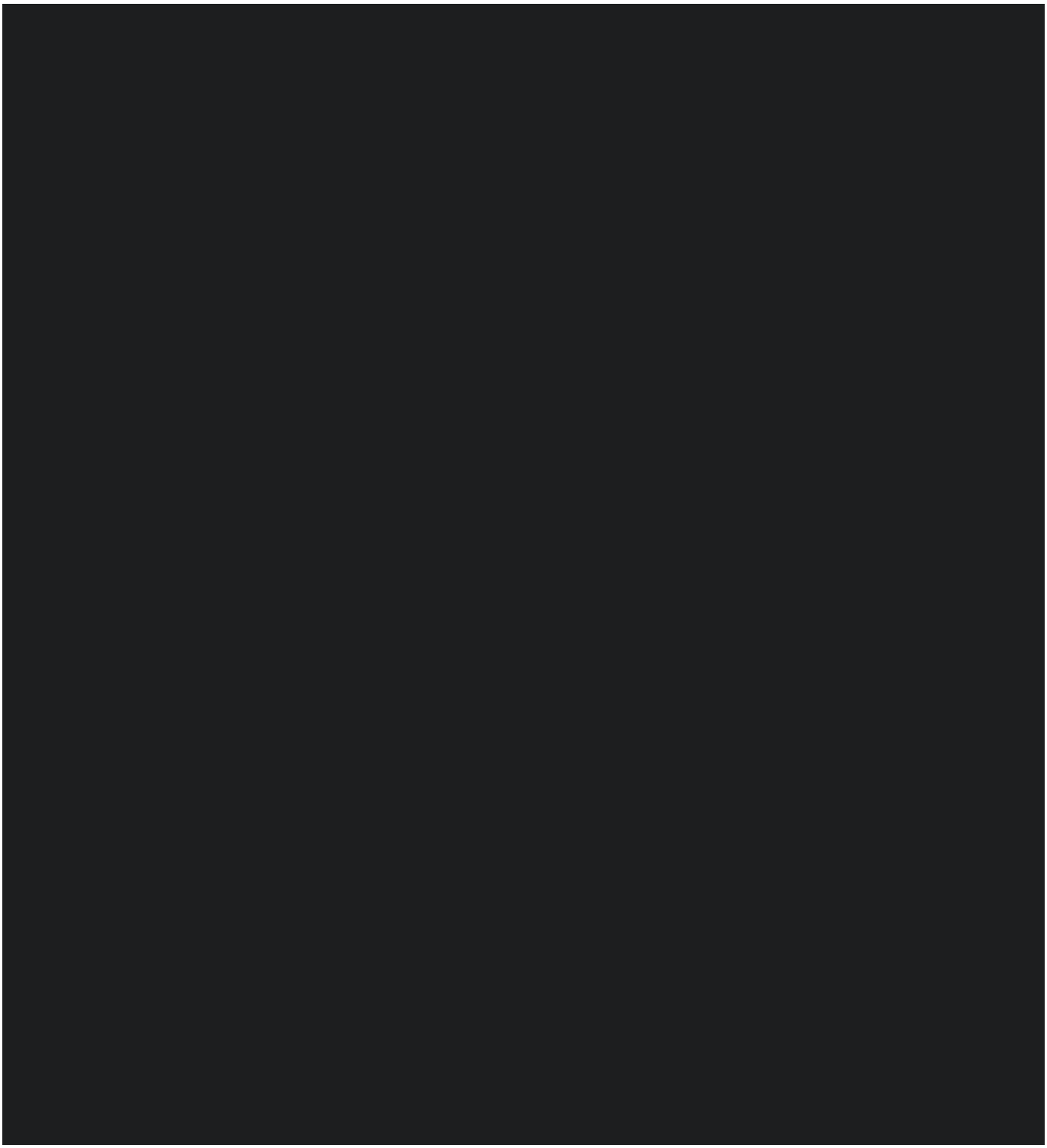
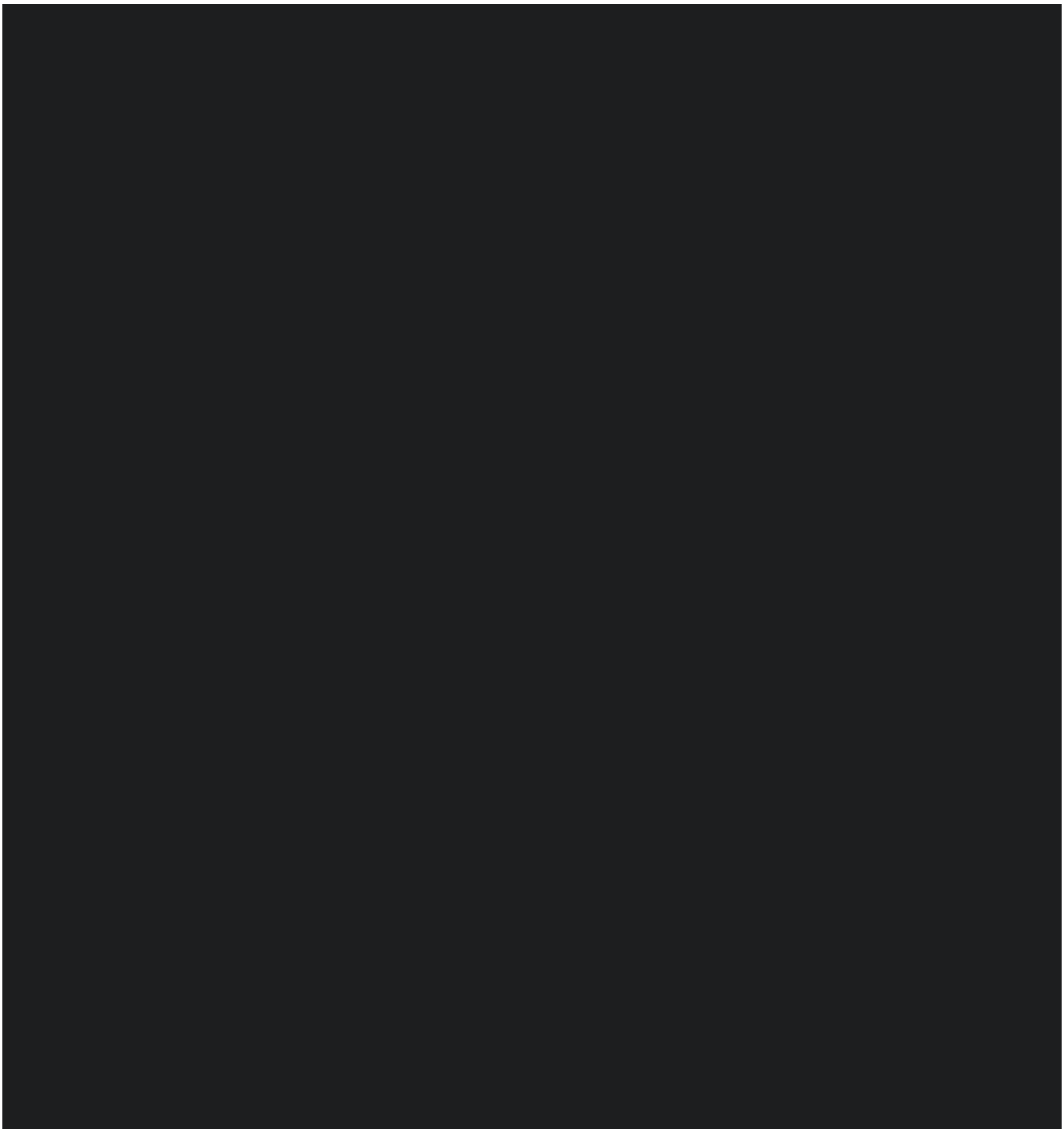
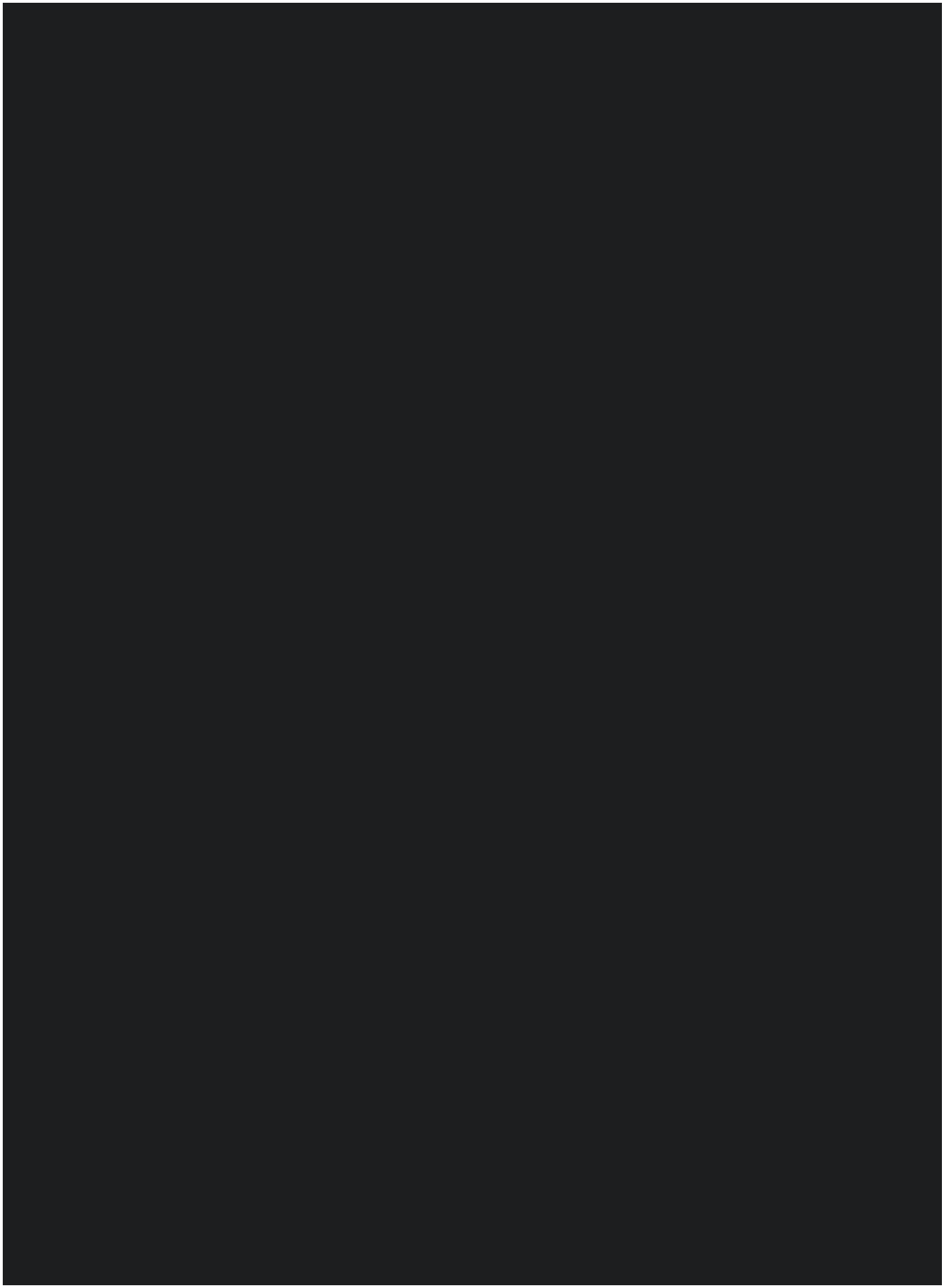
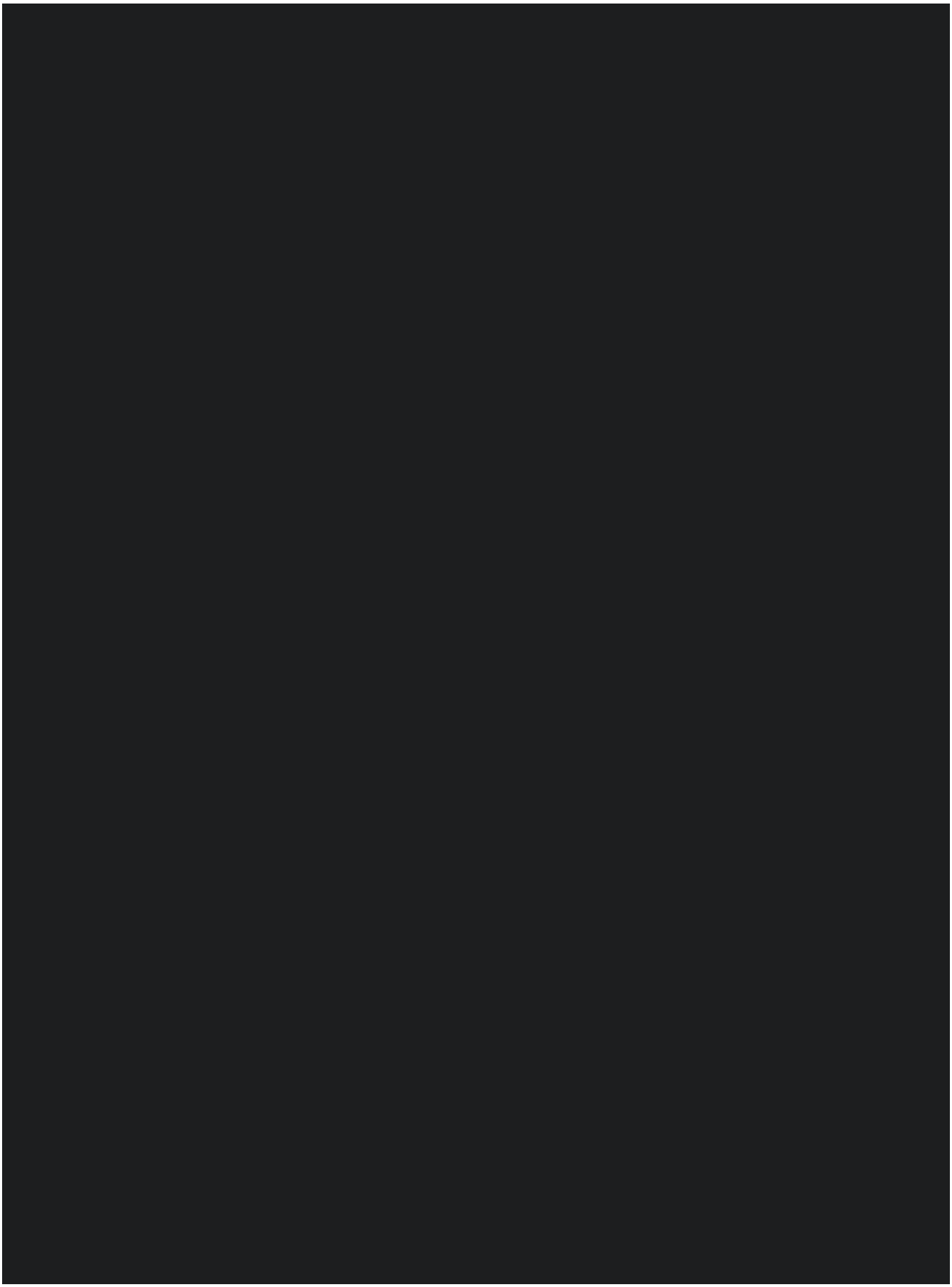
APPENDIX A: PATIENT REPORTED OUTCOMES (STUDY QUESTIONNAIRES)

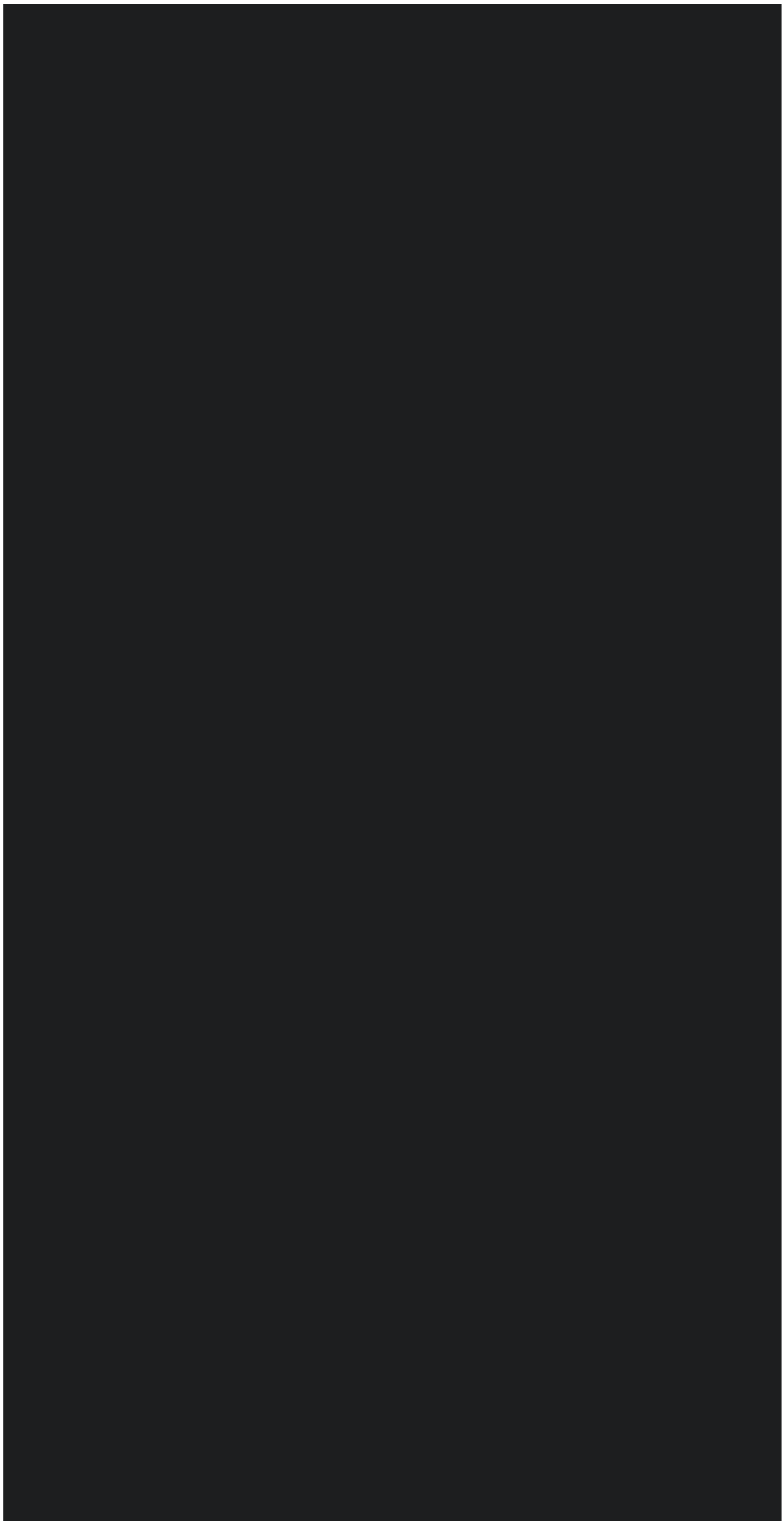


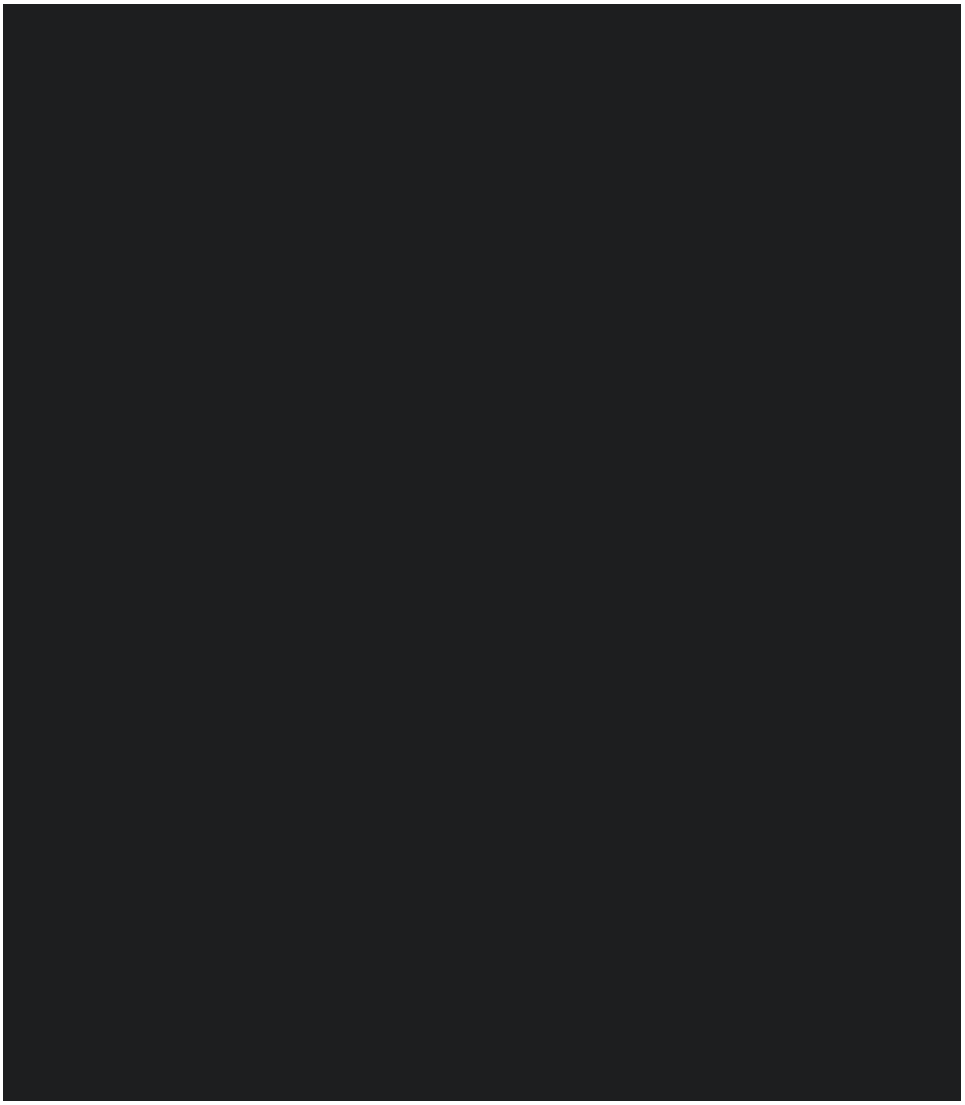












APPENDIX B: PATIENT INSTRUCTION GUIDE

A patient instruction guide (PIG) 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
Blink is a trademark of Johnson & Johnson Surgical Vision, Inc.

No. 93286BT
AM60870US12C
9587X
Revision Date: 07/2018

APPENDIX D: NON-INVASIVE TEAR BREAK-UP TIME (NIBUT) MEASUREMENT USING THE MEDMONT E300 CORNEAL TOPOGRAPHER WORK AID

Title: **Non-Invasive Tear Break-Up Time (NIBUT) Measurement using the Medmont E300 Corneal Topographer Work Aid**

Document Type: [redacted]

[redacted]

Title: Non-Invasive Tear Break-Up Time (NIBUT) Measurement using the Medmont E300 Corneal Topographer Work Aid

Document Type: [redacted]

[redacted]

Title: **Non-Invasive Tear Break-Up Time (NIBUT) Measurement using the Medmont E300 Corneal Topographer Work Aid**

Document Type: [redacted]

[redacted]

Title: **Non-Invasive Tear Break-Up Time (NIBUT) Measurement using the Medmont E300 Corneal Topographer Work Aid**

Document Type: [redacted]

[redacted]

[redacted]

[redacted]

APPENDIX E: [redacted]

- [redacted] EXPANDED SODIUM FLUORESCEIN CORNEAL STAINING
- [redacted] SUBJECT REPORTED OCULAR SYMPTOMS/PROBLEMS
- [redacted] DETERMINATION OF DISTANCE SPHEROCYLINDRICAL REFRACTIVE ERROR
- [redacted] BIOMICROSCOPY SCALE
- [redacted] DISTANCE AND NEAR SNELLEN VISUAL ACUITY EVALUATION
- [redacted] PATIENT REPORTED OUTCOMES

[redacted] EXPANDED SODIUM FLUORESCEIN CORNEAL STAINING

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] SUBJECT REPORTED OCULAR SYMPTOMS/PROBLEMS

[redacted]

[redacted] DETERMINATION OF DISTANCE SPHEROCYLINDRICAL REFRACTIVE ERROR

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] BIOMICROSCOPY SCALE

Title:	**Biomicroscopy Scale**
Document Type:	[redacted]
Document Number:	[redacted] **Revision Number: 10**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Title:	**Biomicroscopy Scale**
Document Type:	[redacted]
Document Number:	[redacted] **Revision Number: 10**

[redacted]

[redacted] DISTANCE AND NEAR SNELLEN VISUAL ACUITY EVALUATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] PATIENT REPORTED OUTCOMES

Title: Patient Reported Outcomes
Document Type: [redacted]
Document Number: [redacted] **Revision Number:** 3

[redacted]

APPENDIX F: [redacted] GUIDELINES FOR COVID-19 RISK MITIGATION

1.0 PURPOSE

The purpose of this document is to provide guidelines for the re-opening or initiation of clinical study sites participating in Johnson & Johnson Vision Care, Inc. (JJVCI) clinical studies during the COVID-19 pandemic.

2.0 SCOPE

This document provides guidelines for Johnson & Johnson Vision Care (JJVCI) to address the potential risks from COVID-19 to study subjects, investigators, study site staff, and monitors at study sites. The guidance provided in this document is in effect from the date of approval through the date of retirement of this Work Instruction. At a minimum, this Work Instruction will be reviewed and updated on a quarterly basis, as appropriate.

NOTE: Re-opening of sites outside of the US will be evaluated on a country by country basis subject to local health authority guidance.

3.0 DEFINITIONS

American Academy of Optometry (AAO): The American Academy of Optometry is an organization of optometrists based in Orlando, Florida. Its goal is to maintain and enhance excellence in optometric practice, by both promoting research and the dissemination of knowledge. The AAO holds an annual meeting, publishes a monthly scientific journal, gives credentials to optometrists through the fellowship process and publishes position statements.

American Optometric Association (AOA): The American Optometric Association, founded in 1898, is the leading authority on quality care and an advocate for our nation's health, representing more than 44,000 Doctors of Optometry (O.D.), optometric professionals, and optometry students. Doctor of Optometry take a leading role in patient care with respect to eye and vision care, as well as general health and well-being. As primary health care providers, Doctor of Optometry have extensive, ongoing training to examine, diagnose, treat and manage ocular disorders, diseases and injuries and systemic diseases that manifest in the eye. The American Optometric Association is a federation of state, student, and armed forces optometric associations. Through these affiliations, the AOA serves members consisting of optometrists, students of optometry, paraoptometric assistants and technicians. The AOA and its affiliates work to provide the public with quality vision and eye care.

Centers for Disease Control and Prevention (CDC): The Centers for Disease Control and Prevention is a national public health institute in the United States. It is a United States federal agency, under the Department of Health and Human Services, and is headquartered in Atlanta, Georgia.

COVID-19: Current outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

Clinical Study: Voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments. May also be called clinical trials, studies, research, trials, or protocols.

Clinical Study Site: Location where a clinical study is conducted, such as a doctor's office, university, or laboratory. Clinical studies are conducted by Investigators who are individual(s) responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals, the Investigator is the responsible leader of the team and may be called the Principal Investigator.

Clinical Operations Manager (COM): The Johnson & Johnson Vision Care (JJVCI) individual responsible for the overall management of a clinical trial.

Monitor: An individual designated to oversee the progress of a clinical study and ensure that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

Medical Safety Officer (MSO): Physician who has primary accountability in their product portfolio for product health and safety, and who serves as an independent medical voice for patient safety.

Safety Management Team (SMT): A cross-functional, collaborative team responsible for review, assessment and evaluation of medical safety data arising from any source throughout the product life cycle.

4.0 GUIDANCE FOR STUDY DOCUMENTS

In alignment with recent health authority guidance, JJVCI is providing recommendations for study-related management in the event of disruption to the conduct of the clinical study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health, safety and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted as outlined in the protocol.

During the COVID-19 pandemic, the additional risks listed below need to be considered for study participants and study personnel:

4.1 Additional Risks Related to the COVID-19 Pandemic:

- The possible transmission of the Coronavirus infection and consequent complications, beyond the risk of adverse events due to the investigational device and/or procedures.
- The risk may be higher in an optometric clinical study because of the close contact the subject will have with health care professionals during the procedures and assessments (since the investigator must make the measurements close to the subject's face) and, in addition the need for multiple follow-up visits/exams which may expose the subject to other patients and/or healthcare professionals who might be transmitting the virus, even if they do not have symptoms.
- Potential disruptions to the study may be necessary due to current or future pandemic-related emergency restrictions, which may lead to delays in scheduled follow-up visits.
- Subjects experiencing an adverse event related to contact lens wear may receive delayed treatment due to COVID-19 restrictions. In this event, all assessments that can be conducted virtually will be completed by the investigator to determine the best course of treatment for the subject, including an unscheduled visit, up to discontinuation from the study, as appropriate.

If a study subject is found to have contracted COVID-19 during participation in a study, he/she will be discontinued from the study and followed until COVID-19 Adverse Event (AE) resolution.

To help minimize the above potential risks, JJVCI recommend reviewing/complying with local, state, and governmental guidance for COVID-19 risks.

JJVCI will provide the following study specific documents with language pertaining to COVID-19 risks:

4.1.1 Informed Consent:

Will include information concerning the study-associated risks related to the COVID-19 pandemic in bold font and/or boxed on the first page of the Informed Consent document:

STUDY ASSOCIATED RISKS RELATED TO COVID-19 (CORONAVIRUS) PANDEMIC

It is important to note that this study will be conducted, at least in part, during the COVID-19 pandemic. As such, additional risks associated with the infection with COVID-19 exist for you. This is particularly important for this study due, in part, to the closeness of the doctor during the study examinations.

The potential effects of the disease are not fully known, at this time, and may include long-term serious health consequences. In severe cases, this may result in hospitalization and/or death. Based on current knowledge from the Centers for Disease Control and Prevention (CDC), those at high-risk for severe illness from COVID-19 include older adults and people with underlying medical conditions.

During this study, all appropriate measures will be taken to minimize risks including the use of personal protective equipment such as masks and gloves, as well as proper sanitization. This is in conformance to guidance from the CDC, local health departments, and the state and county in which the study doctor's office is located. However, these measures may not completely eliminate the risks associated with contracting COVID-19.

If you are found to have contracted COVID-19 or feel ill with flu-like symptoms during participation in the study, you will not be permitted to continue in-office study follow-up visits, but you will receive instructions and your condition will be monitored by the doctor and/or study staff.

4.1.2 COVID-19 Risk Control Checklist (Attachment-B):

Will include COVID-19 risk control methods that are required by a site to conduct JJVCI clinical studies. The risk controls are consistent with CDC, AOA, AAO Guidance. The Principal Investigator will review/sign the study specific checklist prior to the Site Initiation Meeting.

4.1.3 Protocol Compliance Investigator(s) Signature Page:

Will include a statement indicating that the Principal Investigator (PI) agrees to conduct the study in compliance with all local, state, and governmental guidance's for COVID-19 risk mitigation.

I have read the suggested guidance provided by JJVCI pertaining to the COVID-19 risk mitigation, (COVID-19 Work Instruction in the Appendix of this protocol). I agree to conduct this study in compliance with local, state, governmental guidance for COVID-19 risks.

4.1.4 Study Site Initiation Training Slides:

Will include suggestions to help mitigate potential transmission of COVID-19. Suggestions may include maintaining social distancing in the clinical site by staggered scheduling of study patients, wearing proper PPEs, frequent disinfection, and installing shields on the slit lamp and other applicable equipment.

5.0 GUIDANCE FOR REMOTE SUBJECT VISITS

Potential disruptions to the study may be necessary due to current or future pandemic-related emergency restrictions. Possible disruption of the study as a result of COVID-19 control measures may lead to delays in scheduled follow-up visits.

Subjects may be delayed in being seen for study follow up visit(s), for example due to COVID-19 control measures or due to the subject's concerns or fears about COVID-19 risk. When appropriate, the remote assessment will be conducted to the extent possible. Discussions with the subject during remote assessments may include:

Procedure	Details
Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire regarding the test article when applicable and feasible.
Change of Medical History (Adverse Events) and Concomitant Medications / Therapies Review	Record any adverse events or medical history changes from the previous study visit with the subject/parents. Review the subject's concomitant medications/therapies and record any changes from the previous study visit.
Wearing Time and Compliance	Record the average wearing time (including number of hours per day during weekdays and weekends, and number of days per week). Confirm compliance with the prescribed wear schedule. • Record and discuss the lens wear compliance based on the subject's self-report. For example, the subjects will be asked the time of the day the subject typically puts on the study lenses in the morning and takes off in the evening, the number of days per week lenses were worn, and the number of consecutive days the subject didn't wear the study lenses, etc.

The discussion with the subject will be documented in EDC under Tele-Visit and a minor protocol deviation will be noted. If during the telephone consultation, a subject states he/she wishes to discontinue participating in the study, instruct the subject to stop wearing the study lenses and schedule the subject to return to the clinic for a Final Evaluation at the at earliest possible time. Subjects should return all unused lenses to the clinic at the last visit.

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing data, including data related to protocol-specified procedures. Case report forms should capture specific information regarding the basis of missing data, including the relationship to the COVID-19 pandemic.

6.0 STUDY CONDUCT DURING PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including Optometry Clinics; and changes in clinic procedures required to address the COVID-19 challenge.

Every effort should be made to adhere to protocol-specified assessments for study participants, including follow-up. However, if scheduled visits cannot be conducted in person at the study site it is suggested that assessments be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed in order to continue participant monitoring in accordance with the protocol where possible. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible.

Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Interruptions of test article wear or discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical monitor to discuss initial plans for study intervention and follow-up. The medical monitor will notify the Safety Management Team of any subject(s) that have reported "COVID-19", "Asymptomatic COVID-19", or "Suspected COVID-19" adverse events within 24 hours of the notification.

Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

COVID-19 screening procedures that may be mandated by local healthcare systems do not need to be reported as an amendment to the protocol even if done during clinical study visits.

6.1 Monitoring Visits

When on-site monitoring by the sponsor is not feasible, the sponsor's site monitor will contact the study site to schedule remote visits. In such cases, on-site monitoring visits will resume when feasible, with increased frequency to address the source data verification backlog.

Even with staffing limitations during this COVID-19 pandemic, all routine operations related to clinical trials should be well-documented and archived as part of standard process. When conditions permit, all parties involved in this clinical trial should communicate relevant information in a timely manner so that all relevant parties remain sufficiently informed.

6.1.1 Study Site Initiation:

During the period that this Work Instruction is in effect, Site Initiation Meetings and training of study site staff will be conducted remotely. The JJVCI study team will conduct training via Skype, Zoom, Microsoft Teams or similar software as well as utilize online training materials, as applicable. Study site training will be documented utilizing Site Initiation Report [redacted] per Study Site Initiation [redacted]

On-site visits may be considered when, for example, hands-on training or evaluation of site facilities is required. While on site, the Clinical Research Associate (CRA) will follow all local, state, and governmental policies for COVID-19 Risk Mitigation, including social distancing, wearing of PPE, etc. as applicable for the location of the study site.

6.1.2 Interim Monitoring Visits (if applicable):

During the period that this Work Instruction is in effect, Interim Monitoring On-site visits will be kept to a minimum and include only those tasks that the CRA cannot perform remotely (e.g., source document verification, test article reconciliation, etc.).

To ensure data integrity during the conduct of all JJVC studies, clinical study teams will follow the study specific Clinical Monitoring Plan [redacted]

While on site, the CRA will follow all local, state, and governmental policies for COVID-19 Risk Mitigation, including social distancing, wearing of PPE, etc. as applicable for the location of the study site.

6.1.3 Study Site Closure:

During the period that this Work Instruction is in effect, the duration of the Study Site Closure Visit will be limited to tasks that the CRA cannot perform remotely (e.g., source document verification, test article final reconciliation and return, etc.).

Attachment A: Study Site Correspondence

XXXX XX, 2020

Re: COVID-19 Mitigation Plan, <<CR-xxxx/protocol title>>

Dear <<Principal Investigator>> and Study Team,

Coronavirus (COVID-19) has impacted several communities and business activities over the past several months. While we work toward the successful conduct of clinical studies, our commitment continues to be the safety of patients, healthcare professionals, and to our communities.

Therefore, we would like to share the following revisions/additions related to the above referenced Johnson & Johnson Vision Care company sponsored clinical trial(s) you are currently working on or considering participation within.

Protocol:

- Guidelines for COVID-19 Risk Mitigation provided in the Appendix section.

Protocol Signature Page:

- Will include a statement indicating the Principal Investigator agrees to conduct the study in compliance with all local, state, and governmental guidelines for COVID-19 risk mitigation.

Informed Consent:

- Will include information concerning the study-associated risks related to the COVID-19 pandemic in bold font and/or boxed on the first page of the Informed consent document.

COVID-19 Risk Control Checklist for Clinical Studies:

- Will include COVID-19 risk control measures that are required to ensure the safety and health of subjects, site staff and monitors during the pandemic.

We want to encourage the need for open lines of communication about potential challenges you may foresee as the result of the current COVID-19 situation. Therefore, we encourage you to regularly connect with your respective Johnson & Johnson clinical study team (Clinical Research Associate (CRA), Lead CRA or Study Managers).

Thank you for your continued engagement, collaboration, and dedication to your study subjects during this challenging time.

Please file this letter in your site file study correspondence.

Attachment B: COVID-19 Risk Control Checklist

Study Number
Site Number
Principal Investigator (PI) Name

The following COVID-19 risk control methods are required to conduct Johnson & Johnson Vison Care clinical studies. Please review the following requirements and Initial each requirement.

PI Initials	General Site Safety Planning Measures
	Signage within site describing Risk Control methods
	Social Distancing practices throughout site (waiting rooms, lobby, exam rooms, etc.)
	Non-contact thermometer available to assess temperatures of staff and patients
	Training on patient flow and physical distancing in waiting room
	Establish longer time frame between patient appointments to reduce persons in the site
	Staff should receive job-specific training on PPE and demonstrate competency with selection and proper use of PPE and wear at all times during interactions with subjects (e.g., putting on and removing without self-contamination)

PI Initials	Site Staff Daily Safety Measures
	As part of routine practice, site staff should regularly monitor themselves for fever and symptoms of COVID-19, including temperature checks
	Any staff member (including non-study clinic staff and Investigators) showing signs of being sick or testing positive for COVID-19 must not be permitted to work on activity that may expose study related staff and subject and the Sponsor shall be informed **NOTE: Inform JJVC in 24 hours of any COVID-19 cases and all potential exposure during the clinical study.**
	Ensure that all staff wear a mask Gloves should be required when working directly with patients and changed between each patient
	Have staff thoroughly wash hands for at least 20 seconds or use an alcohol-based hand sanitizer when they arrive, before and after each patient, before eating and after using the bathroom.
	Cleaning and disinfection procedures for exam rooms and instruments or equipment between patients with gloves.
	Cleaning and disinfection procedures for commonly touched surfaces (doors, chairs, computers, phones, etc.) with gloves.

PI Initials	Before a Patient or Study Visit:
	Patients should be asked prior to entering the site about fever and respiratory illness and whether they or a family member have had contact with another person with confirmed COVID-19 in the past 14 days. Patients exhibiting signs of being sick should be rescheduled when their symptoms resolve.
	Instruct patients that companions should remain outside of the facility and not accompany the patient into the facility unless they are a parent/guardian of the patient or if they are a true caregiver and need to assist the patient
	Request the patient to call or text the office upon arrival so entrance to and movement through facility can be coordinated by site staff

PI Initials	Patients Entering the site:
	Temperature checks utilizing a non-contact thermometer for all patients and companions entering the site.
	All patients and companions must wear cloth or disposable mask at all times in the site
	Maintain social distancing. Waiting rooms or lobbies should be as empty as possible. Advise seated patients to remain at least 6 feet from one another.
	Communal objects in (e.g. toys, reading materials, etc.) should be removed or cleaned regularly.

I certify that I have read and agree to implement all the listed COVID-19 Risk Control Measures required for the conduct of Johnson & Johnson Vision Care studies.

Principal Investigator Signature and Date

RESOURCE LINKS

US Resource Links

- OSHA Training
  https://www.osha.gov/SLTC/covid-19/controlprevention.html

  Personal Protective Equipment (PPE) Training
  CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html

- I&R Training
  ACUVUE® LensAssist: https://www.acuvue.com/lensassist

- Clinic Preparedness Guides
  CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinic-preparedness html
  AOA: https://aoa.uberflip.com/i/1240437-aoa-guidance-for-re-opening-practices-covid·19/1?m4=
  American Optometric Association: https://www.aoa.org/optometry-practice-reactivation-preparedness-guide

- ln-Office Disinfection of Multi-Patient Use Diagnostic Contact Lenses
  https://www.gpli.info/wp-content/uploads/2020/03/2020-01-15-in-office-disinfecting-of-diagnostic-lenses.pdf

OUS Resource Links

- Updates on local regulations in Hong Kong
  https://www.coronavirus.gov hk/eng/index.html

- Resumption of optical services in England: Letter from Matt Neligan and Poonam Sharma
  https://www.england nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0601-reopening-of-optical-services-letter-17-june-2020.pdf

- NHS Optical Letter
  https://www.england nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0127-optical-letter-1-april-2020.pdf

- The College of Optometrists primary eye care COVID-19 guidance: Red phase
  https://www.college-optometrists.org/the-college/media-hub/news-listing/coronavirus-covid-19-guidance-for-optometrists.html

- The College of Optometrists COVID-19: College updates
  https://www.college-optometrists.org/the-college/media-hub/news-listing/coronavirus-2019-advice-for-optometrists.html#CollegeGuidelines

- Infection Control Guidelines. (n.d.). Retrieved from Canadian Association Of Optometrists: https://opto.ca/sites/default/files/resources/documents/infection_control_guidelines_2016.pdf

- Infection prevention and control for COVID-19: Interim guidance for outpatient and ambulatory care settings. (2020, May 23 May). Retrieved from Government of Canada: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/interim-guidance-outpatient-ambulatory-care-settings html

- Information for Members On Coronavirus (COVID-19). (n.d.). Retrieved from Canadian Association Of Optometrists: https://opto.ca/sites/default/files/resources/documents/information_for_members_on_coronavirus.pdf

- Coronavirus (COVID-19) resources for health professionals, including aged care providers, pathology providers and health care managers. (2020, September 24). Retrieved from Australian Government Department of Health: https://www health.gov.au/resources/collections/coronavirus-covid-19-resources-for-health-professionals-including-aged-care-providers-pathology-providers-and-health-care-managers

- Environmental Cleaning and Disinfection Principles for COVID-19. (n.d.). Retrieved from Australian Government Department of Health: https://www.health.gov.au/sites/default/files/documents/2020/03/environmental-cleaning-and-disinfection-principles-for-covid-19.pdf

- Infection control guidelines and advice. (n.d.). Retrieved from Optometry Australia : https://www.optometry.org.au/practice-professional-support/coronavirus-covid-19-what-optometrists-need-to-know/covid-19-clinical-advice/infection-control-guidelines-and-advice/

PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE

Protocol Number and Title: CR-6502 Clinical Evaluation of a Multidose Preservative-free Lubricating Eye Drops Contained in Novelia® Eye Dropper in Non-Contact Lens Wearing Patients

Version and Date: 3.0 25 April 2023

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

I agree to conduct this study according to ISO 14155:2020,[1] the Declaration of Helsinki,[2] United States (US) Code of Federal Regulations (CFR)[3], and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations. I, as the Principal Investigator, am responsible for ensuring that all clinical site personnel, including Sub-Investigators, adhere to all 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.

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.

I have read the suggested guidance provided by JJVCI pertaining to the COVID-19 risk mitigation, (COVID-19 Work Instruction in the Appendix F of this protocol). I agree to conduct this study in compliance with local, state, governmental guidance for COVID-19 risks.

Principal Investigator: _____ _____
Signature Date

_____
Name and Professional Position (Printed)

Institution/Site: _____ _____
Institution/Site Name

_____ _____
Institution/Site Address