Study Protocol

Clinical Investigation of the Bacterially-Derived Healon EndoCoat PRO Ophthalmic Viscosurgical Device (OVD)

PROTOCOL NUMBER: VSCO-110-LOKE

NCT Number: NCT 05575063

Document Date: March 01, 2024

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Clinical Investigation of the
Bacterially-Derived Healon EndoCoat PRO Ophthalmic Viscosurgical Device
(OVD)

IDE Number: G220153

PROTOCOL NUMBER: VSCO-110-LOKE

SPONSOR: Johnson & Johnson Surgical Vision, Inc.
31 Technology Dr., Suite 200
Irvine, CA 92618

Investigator Agreement

As an Investigator, I agree to :

- Implement and conduct this study diligently and in strict compliance with this agreement; the protocol; Good Clinical Practices; 21CFR812, ISO 14155 and all other applicable FDA regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB), FDA or other regulatory authorities; and all other applicable laws and regulations.
- Supervise all testing of the device where human subjects are involved.
- Ensure that the requirements for obtaining informed consent are met.
- Obtain authorization for use/disclosure of health information (e.g., HIPAA authorization or equivalent).
- Maintain all information supplied by Johnson & Johnson Surgical Vision in confidence and, when this information is submitted to an independent IRB or any other group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date

PERSONNEL AND FACILITIES

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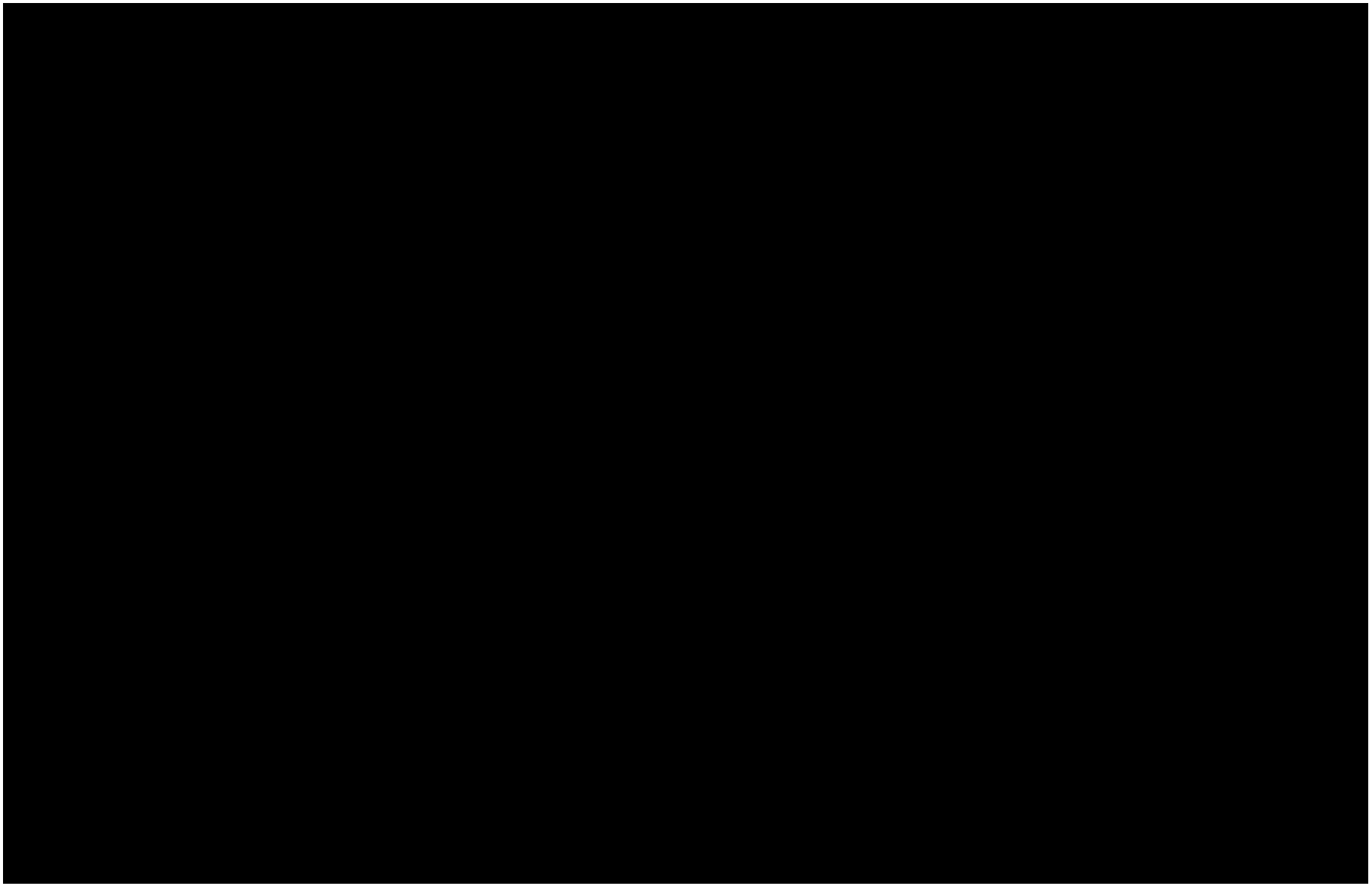

1. SYNOPSIS

PROTOCOL:	Clinical Investigation of the Bacterially-Derived Healon EndoCoat PRO Ophthalmic Viscosurgical Device (OVD) Protocol Number: VSCO-110-LOKE
STUDY TREATMENTS:	Test Product: Healon EndoCoat PRO ("EndoCoat PRO") (Johnson & Johnson Vision) Control Product: Commercially-available Healon EndoCoat ("EndoCoat") (Johnson & Johnson Vision)
STUDY OBJECTIVE:	The purpose of this clinical trial is to evaluate the safety and effectiveness of the Healon EndoCoat PRO OVD as compared to the Healon EndoCoat OVD.
CLINICAL HYPOTHESIS:	The Healon EndoCoat PRO OVD will be statistically non-inferior to the currently-available Healon EndoCoat OVD with regard the cumulative rate of IOP spikes ≥ 30 mmHg and mean endothelial cell count (ECC) change at 3 months postoperatively.

OVERALL STUDY DESIGN:

Structure:	Prospective, multicenter, paired-eye, randomized, subject/evaluator-masked clinical investigation of the Healon EndoCoat PRO OVD versus the current Healon EndoCoat OVD control.
Number of sites:	Up to 10 sites in the USA.
Duration:	3 months
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

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Number of Subjects: Up to 195 subjects will be enrolled [redacted]

Inclusion Criteria (all criteria apply to each study eye):

- Minimum 22 years of age
- Cataracts for which extraction and posterior chamber IOL implantation have been planned in both eyes
- Potential for postoperative best corrected distance visual acuity (BCDVA) of 20/40 Snellen or better
- Clear intraocular media, other than cataract
- Availability, willingness, and sufficient cognitive awareness to comply with examination procedures
- Signed informed consent and HIPAA authorization

Exclusion Criteria (all criteria apply to each study eye):

- Pupil abnormalities (non-reactive, fixed pupils, or abnormally shaped pupils)
- Recent ocular trauma or ocular surgery that is not resolved/stable or may affect clinical outcomes or increase risk to the subject
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level worse than 20/40 Snellen during the study.
- Prior, current, or anticipated use during the course of the 3-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcome or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery)
- Conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration or tilt, such as pseudoexfoliation, trauma, or posterior capsule defects
- Use of systemic or ocular medications that may affect vision or IOP
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies that are predicted to cause visual acuity losses to a level worse than 20/40 Snellen during the study, or in the opinion of the investigator, may confound the outcome(s) of the study
- Poorly-controlled diabetes
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.).

- Known steroid responder
- Ocular hypertension of ≥ 20 mmHg, medically-controlled ocular hypertension (regardless of IOP value), or glaucomatous changes in the optic nerve
- Endothelial cell count (ECC) lower than 1800 cells/mm^2 preoperatively (based on the average of the three cell counts as taken by the Konan Specular Microscope)
- Known ocular disease or pathology that may affect visual acuity or that may be expected to require retinal laser treatment or other surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.)
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes
- Concurrent participation or participation within 60 days prior to preoperative visit in any other clinical trial

[redacted]

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DATA ANALYSIS:

The investigational OVD will be compared to the control OVD. The 3-month postoperative visit is the key analysis time point for cumulative IOP spikes and ECC.

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2. BACKGROUND/INTRODUCTION

Viscoelastic devices are indicated for use as a surgical aid in anterior segment procedures including cataract surgery with or without an intraocular lens, secondary intraocular lens implantation, corneal transplant surgery, and glaucoma filtration surgery. Some established benefits of using viscoelastic materials in cataract surgery are endothelial cell protection and maintenance of intraocular space.[1] The protection these materials provide result in reduced trauma to the cornea from inadvertent "touch" during intraocular surgery, therefore minimizing endothelial cell loss.[2]

Viscoelastic devices traditionally have been produced using animal-derived components but the use of animal-derived components have been losing favor in many parts of the world. JJSV has transitioned most of their OVDs to bacterially-derived NaHA (i.e., Healon5 PRO) with Healon EndoCoat being the remaining OVD that utilizes animal-derived components. The OVD under investigation is an animal-free, bacterially-derived sodium hyaluronate version of the currently available, bacterially-derived Healon EndoCoat, which is named Healon EndoCoat PRO. This clinical study will evaluate the performance of the bacterially-derived Healon EndoCoat PRO OVD under normal-use conditions during the cataract surgical procedure.

3. CLINICAL HYPOTHESIS

The Healon EndoCoat PRO OVD will be statistically non-inferior to the currently available Healon EndoCoat OVD with regard to the cumulative rate of IOP spikes ≥ 30 mmHg and mean endothelial cell count (ECC) change at 3 months postoperatively.

4. STUDY DESIGN

This study is a 3-month, prospective, multicenter, paired-eye, two-armed, masked, randomized clinical investigation of the bacterially-derived Healon EndoCoat PRO versus the currently available, Healon EndoCoat control.

The study will be conducted at up to 10 sites in the USA and will include 195 enrolled subjects [redacted] Subjects will be randomly assigned to receive the test OVD in one eye and the control OVD in the fellow eye.

[redacted]

[redacted]

5. ACRONYMS

The following acronyms are used throughout the document:

- OVD: Ophthalmic viscosurgical device
- ECC: Endothelial Cell Count
- IOP: Intraocular pressure
- BCDVA: Best corrected distance visual acuity
- SAE: Serious Adverse Event
- JJSV: Johnson & Johnson Surgical Vision, Inc.

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this clinical trial is to evaluate the safety and effectiveness of the Healon EndoCoat PRO OVD as compared to the Healon EndoCoat OVD.

6.1 PRIMARY ENDPOINTS

SAFETY: CUMULATIVE RATES OF IOP SPIKES 30 MMHG OR GREATER MEASURED POSTOPERATIVELY

Success criteria: The cumulative rate of IOP spike for the Healon EndoCoat PRO OVD will be statistically non-inferior to that for control eyes using a non-inferiority margin of 10%

EFFECTIVENESS: MEAN PERCENT ECC CHANGE PREOPERATIVELY VS. POSTOPERATIVELY

Success criteria: The mean percent ECC change for Healon EndoCoat PRO will be statistically non-inferior to that for control eyes using a non-inferiority margin of 5%.

[redacted]

- [redacted]
- Monocular BCDVA
- Monocular UCDVA

7. STUDY PRODUCTS

7.1 OPHTHALMIC VISCOSURGICAL DEVICES

The two OVDs used in this study include the investigational, animal-free, bacterially-derived Healon EndoCoat PRO and the commercially available, bacterially-derived Healon EndoCoat control. Both are considered dispersive viscoelastic devices.

Investigational Healon EndoCoat PRO OVD

Healon EndoCoat PRO is a sterile, nonpyrogenic, viscoelastic preparation of a highly purified sodium hyaluronate (NaHA) in a physiological sodium chloride phosphate buffer solution for intraocular use. This polymer is made up of repeating disaccharide units of glucuronic acid and N-acetyl-β-glucosamine. The ophthalmic viscoelastic contains 3% NaHA that is obtained from a bacterial fermentation source and it has a viscosity of approximately 30 - 90 Pas, a molecular weight of 800,000-1,000,000 Daltons, a pH of 6.8 - 7.6 and an osmolarity of 320 mOsm/kg. The HA of the Healon EndoCoat PRO OVD is derived from an animal-free bacteria-fermentation process.

Healon EndoCoat Control OVD

Healon EndoCoat is a sterile, nonpyrogenic, viscoelastic preparation of a highly purified sodium hyaluronate (NaHA) in a physiological balanced salt solution for intraocular use. This polymer is made up of repeating disaccharide units of glucuronic acid and N-acetyl-β-glucosamine. The ophthalmic viscoelastic contains 3% NaHA that is obtained from a bacterial fermentation source and it has a viscosity of approximately 30-62 Pas, a molecular weight of 800,000 Daltons, a pH of 6.8-7.6 and an osmolarity of 320 mOsm/kg. The HA of the current EndoCoat OVD is derived from a bacteria-fermentation process. Although no animal-origin materials remain in the finished product, casein hydrolysate is used as nutrient source of bacterial fermentation. Casein hydrolysate, originating from bovine milk, is an extensively processed and modified material of animal origin.

[redacted]

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8. STUDY POPULATION

All study subjects will be enrolled from the surgical cataract population at up to 10 sites in the USA. Up to 195 subjects will be enrolled [redacted].

[redacted]

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8.1 INCLUSION CRITERIA (ALL CRITERIA APPLY TO EACH STUDY EYE):

- Minimum 22 years of age
- Cataracts for which extraction and posterior chamber IOL implantation have been planned in both eyes
- Potential for postoperative best corrected distance visual acuity (BCDVA) of 20/40 Snellen or better
- Clear intraocular media, other than cataract
- Availability, willingness, and sufficient cognitive awareness to comply with examination procedures
- Signed informed consent and HIPAA authorization

8.2 EXCLUSION CRITERIA (ALL CRITERIA APPLY TO EACH STUDY EYE):

- Pupil abnormalities (non-reactive, fixed pupils, or abnormally shaped pupils)
- Recent ocular trauma or ocular surgery that is not resolved/stable or may affect clinical outcomes or increase risk to the subject
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level worse than 20/40 Snellen during the study.
- Prior, current, or anticipated use during the course of the 3-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcome or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery)
- Conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration or tilt, such as pseudoexfoliation, trauma, or posterior capsule defects
- Use of systemic or ocular medications that may affect vision or IOP
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies that are predicted to cause visual acuity losses to a level worse than 20/40 Snellen during the study, or in the opinion of the investigator, may confound the outcome(s) of the study
- Poorly controlled diabetes
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.).
- Known steroid responder

- Ocular hypertension of ≥ 20 mmHg, medically controlled ocular hypertension (regardless of IOP value), or glaucomatous changes in the optic nerve
- Endothelial cell count (ECC) lower than 1800 cells/mm^2 preoperatively (based on the average of the three cell counts as taken by the Konan Specular Microscope)
- Known ocular disease or pathology that may affect visual acuity or that may be expected to require retinal laser treatment or other surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.)
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes
- Concurrent participation or participation within 60 days prior to preoperative visit in any other clinical trial

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select ophthalmic surgeons who have completed a residency in ophthalmology (or its documented equivalent) and are licensed to practice medicine and perform surgery at his/her investigative site.

Investigators will be selected from surgeons who are experienced in small-incision, phacoemulsification and IOL implantation in cataract patients. All sites are required to have adequate staff support for reporting and subject follow-up, as well as the necessary instrumentation to conduct study testing.

9.2 INVESTIGATOR OBLIGATIONS

Investigators are required to fulfill the following obligations:

- Conduct the study in accordance with the relevant and current protocol. Investigator will only make changes to a protocol after notifying and obtaining approval from JJSV, the FDA or other governing agencies, and the Investigational Review Board (IRB), except when necessary to protect the safety, rights, or welfare of subjects
- Personally conduct and supervise the study
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties
- Be responsible for protecting the rights, safety and welfare of subjects under the investigator's care and be responsible for the control and documentation of the devices under investigation

- Inform patients that the device(s) are being used for investigational purposes and that requirements relating to obtaining informed consent and IRB approval are met according to 21CFR50, 21CFR56, 21CFR812 and all other applicable laws and regulations
- Maintain confidentiality as required by HIPAA or similar laws and regulations
- Shall not obtain written informed consent from any subject to participate or allow any subject to participate before obtaining FDA and IRB approval
- Document in each subject's case history that informed consent was obtained prior to participation in the study as required by 21CFR812
- Report to JJSV and the reviewing IRB any adverse experiences that occur during the course of the study in accordance with applicable laws and regulations
- Maintain adequate and accurate records in accordance with applicable laws and regulations and make available all study documents and subject medical records for inspection by either JJSV, duly authorized regulatory agencies (e.g., FDA) and/or the IRB
- Submit progress reports on the investigation to JJSV and the reviewing IRB at regular intervals, but no less often than yearly as required by 21CFR812.150
- Ensure the IRB that is responsible for initial and continuing review of the study complies with applicable laws and regulations
- Report all changes in research activity and all unanticipated problems involving risks to patients to the IRB and JJSV
- Supervise and permit investigational device use and disposition in accordance with applicable regulations and protocol requirements. Upon completion of enrollment or termination of the study or the investigator's part of the study, or at JJSV's request, return to JJSV any remaining supply of the investigational device
- Provide sufficient accurate financial information to JJSV to allow JJSV to submit complete and accurate certification or disclosure statements as required by 21CFR54. Promptly update this information if any relevant changes occur during the course of the investigation or for up to one year following completion of the study
- Comply with all other obligations of clinical investigators and requirements according to all applicable FDA regulations (e.g., 21CFR812), all other applicable laws and regulations, and all conditions of approval imposed by the reviewing IRB, the FDA and the regulatory agency of the country in which the study is being conducted
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately informed about the protocol, the investigational device, their

study-related duties and functions and agree to fulfill their obligations in meeting the above commitments.

Investigators shall provide adequate time and resources to conduct and report on the study. The Investigator, or delegate, shall notify JJSV of any change in the conduct of the study including changes in study personnel assigned to the study project, location of the investigational device(s), or maintenance of study records, etc.

9.3 INVESTIGATOR APPROVAL

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Study Files/Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV. Study sites will obtain IRB approvals and fulfill any other site-specific regulatory requirements. The investigator is required to report to JJSV within five working days any withdrawal of approval by the reviewing IRB for his/her participation in the investigation.

Prior to the start of subject enrollment, the following documents must be signed and returned to JJSV:

- Confidentiality Agreement
- Clinical Trial Agreement
- Investigator Agreement/Protocol Signature page
- Clinical Investigator Brochure Signature page
- Financial Disclosure form
- Signed and dated copy of investigator's current curriculum vitae
- Copy of the investigator's current medical license
- Hospital/Ambulatory Surgery Center Clinical Study Acknowledgement, if required

By signing the study documents, the investigator agrees to conduct this study according to the obligations above and all other applicable regulatory and legal requirements.

9.4 INVESTIGATOR INFORMATION

Information on the principal investigator at each investigative site, the coordinating investigator, the address details for each investigative site and the emergency contact details for the principal investigator of each site are listed in a separate document - Study Investigator Information.

10. EXPERIMENTAL PLAN

10.1 OVERVIEW

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2020 and all other applicable regional laws and regulations. The study will not begin until regulatory and IRB approvals have been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed.

This study will be a prospective, multicenter, paired-eye, randomized, two-arm, subject- and evaluator-masked clinical investigation conducted at up to 10 sites. Up to 195 subjects will be enrolled to achieve approximately 114 contralaterally-treated and evaluable subjects at 3 months. After informed consent is obtained and confirmation that all inclusion/exclusion criteria are met, the eyes may be randomized.

After signing the informed consent, eyes meeting all inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to receive either the Healon EndoCoat PRO OVD or the Healon EndoCoat OVD control for the first-eye surgery and the other study product for the second-eye surgery. [redacted] All subjects will be examined through 3 months postoperatively [redacted]

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10.3 PREOPERATIVE PROCEDURES

All subjects enrolled in the study must sign the current IRB-approved informed consent document and meet the inclusion/exclusion criteria. The informed consent must be signed before any study-specific examinations are performed, and this must be documented in the source documents.

All preoperative testing for the study must be completed within 60 days prior to the first surgery. Data from routine (non-study-specific) preoperative cataract examinations performed prior to the informed consent process may be included, provided these tests are conducted no more than 60 days prior to the first-eye surgery. If a test/exam is required by the protocol but is not part of routine testing the investigator performs for cataract evaluations, that test/exam is considered to be study-specific and is not to be done until after the informed consent has been signed by the subject. Following the informed consent process, completion of the preoperative study exam, determination that the subject meets all of the required entrance criteria and determination of the first eye to be operated on, the subject may be scheduled for surgery and randomized.

As the Informed Consent Form is signed at the beginning of the preoperative study exam, some subjects may not qualify after study-specific testing is performed. Subjects will be considered screen-failures if they do not qualify or otherwise decide not to proceed with surgery or study participation. These subjects will be exited from the study.

[redacted]

10.4 RANDOMIZATION AND MASKING

A randomization list stratified by investigational sites will be created [redacted] Subjects will be randomly assigned to receive either the Healon EndoCoat PRO or the Healon EndoCoat control in the first operative eye in a 1:1 ratio; subjects will then receive the OVD not used in the first-eye surgery in the fellow eye. Unmasked study personnel at the site will be trained in the randomization process through the EDC system and will randomize subjects as they are enrolled. Randomization will take place after the subject has signed the informed consent document, has met all inclusion and exclusion criteria, and the investigator has documented which eye will be the first to undergo surgery.

As part of the informed consent process, the investigator or delegate will explain to the subject the requirements of a randomized study and the differences between the two OVDs: the Healon EndoCoat PRO investigational OVD and the Healon EndoCoat control OVD.

[redacted]

The subjects, investigators, and the study technicians performing the postoperative exams are to be masked through study completion. [redacted]

Unmasked Clinical Research Associates (CRAs) will visit the site to confirm OVD traceability and to monitor Operative visit forms and source documents. All other JJSV study personnel will remain masked through the final study visits.

10.5 STUDY OVD SUPPLY

The investigational OVD will be obtained from a site consignment that is supplied by the Sponsor following IRB approval for a given site. [redacted]

The control OVD will also be obtained from a site consignment that is provided by the Sponsor specifically for use in the study.

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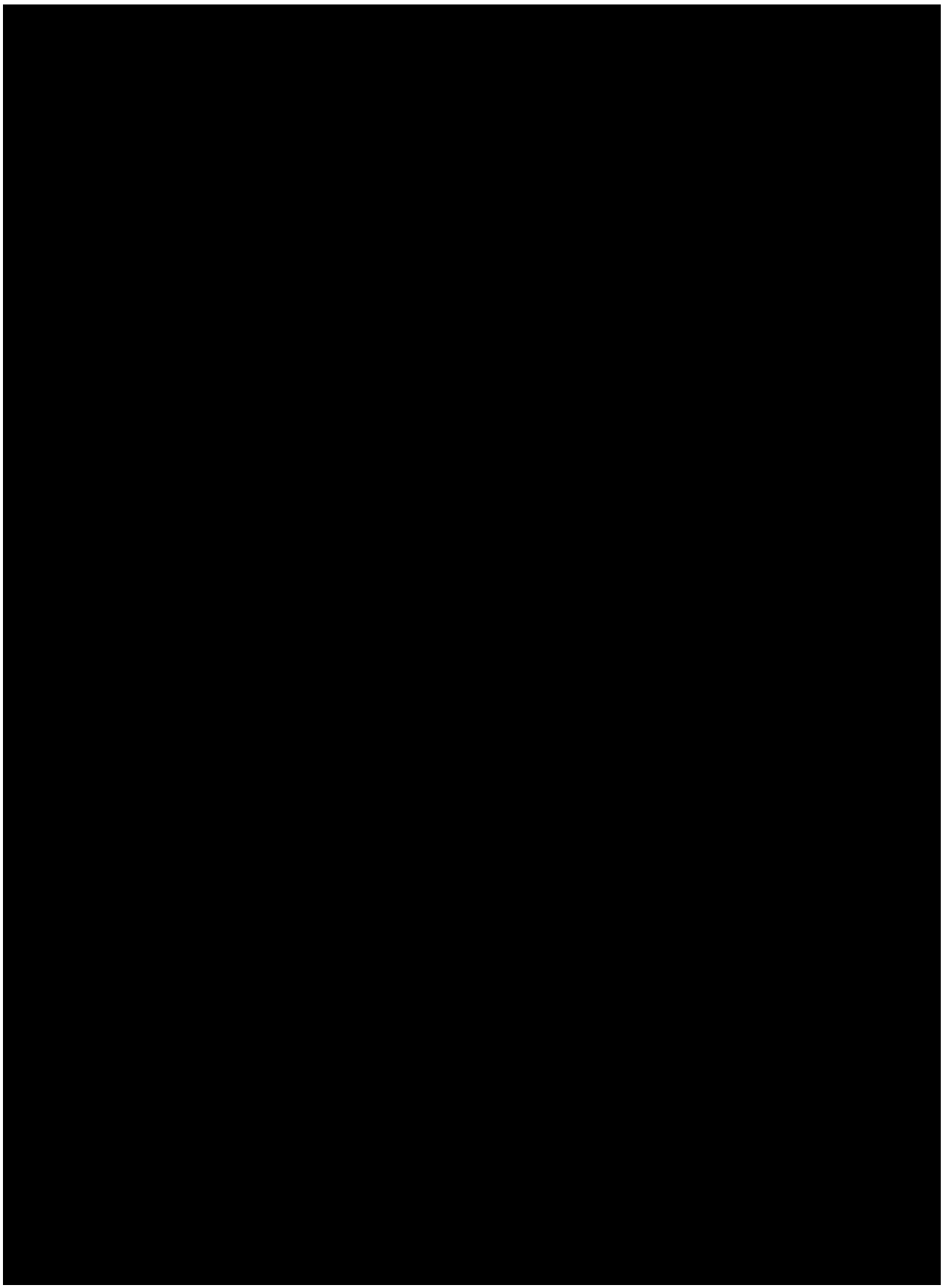
10.7 OPERATIVE PROCEDURES

Both the investigational and the control OVDs should be generally used as the investigator would use his/her standard OVD(s) during the cataract removal and lens implantation procedure. [redacted]



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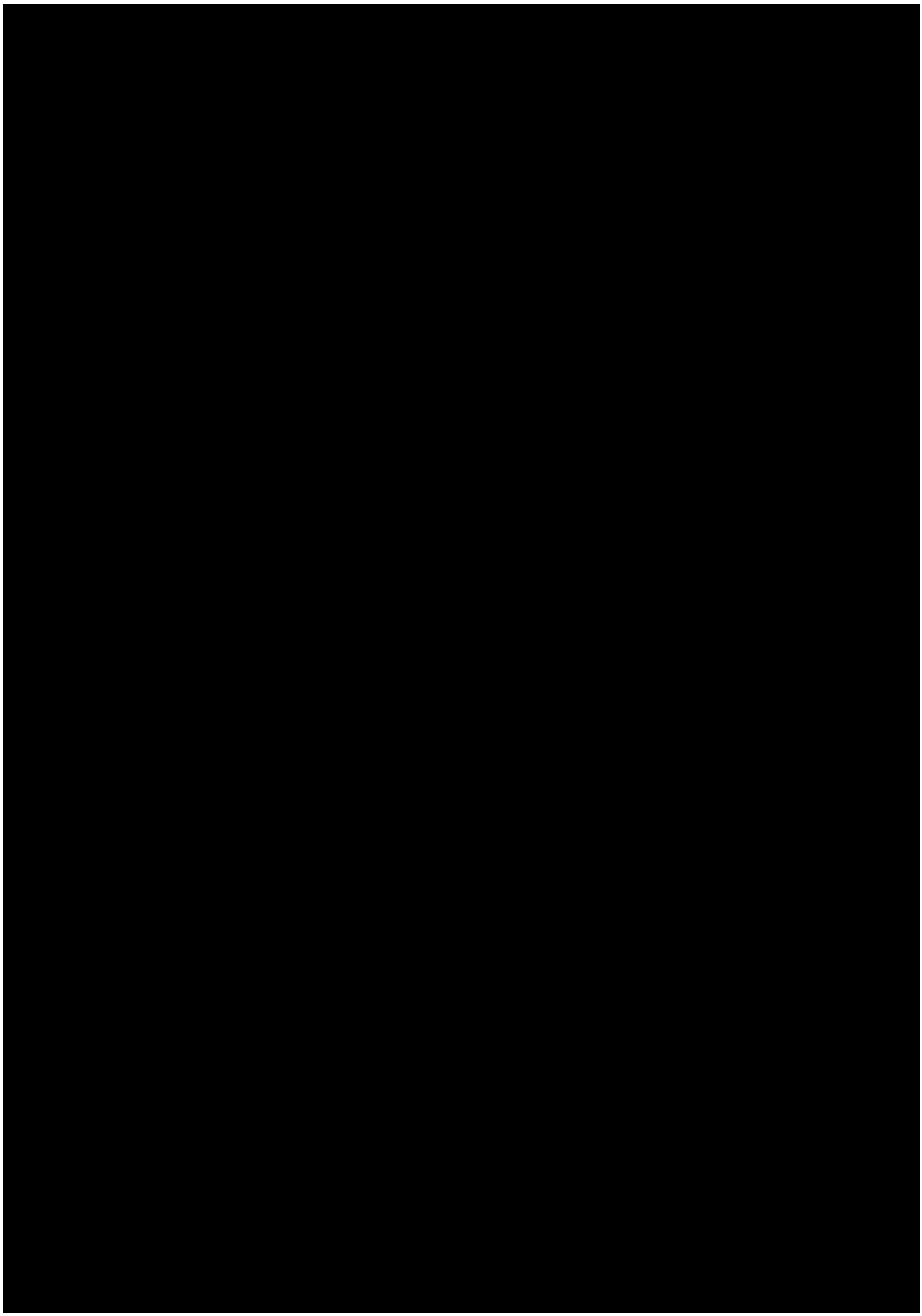
10.8 POSTOPERATIVE PROCEDURES

Postoperatively, subjects will be examined according to the schedule [redacted]



ADVERSE EVENTS

Subjects should be assessed at each visit for occurrence of and/or change in status of any adverse events, particularly serious and/or device-related adverse events.

10.9 EXIT OF SUBJECTS

An Exit Case Report Form will be completed for all subjects, either when they complete the study or if they exit early.

It is the responsibility of the investigator to provide complete follow-up data to JJSV for each subject, and every attempt should be made to gather that complete follow-up data for all subjects enrolled as missing data can have a negative effect on the study results. Patients who would be traveling, relocating or otherwise unavailable for postoperative follow-up visits should not be chosen for this clinical study.

Subjects will be discontinued/early terminated from the study if the subject dies, or if the subject is irretrievably lost for unavoidable reasons such as: subject moved/unable to locate, subject uncooperative/refuses further study participation, subject ill/unable to travel. Documentation of efforts to trace subjects that are lost to follow-up and possible reasons are required. In the event of subject relocation, efforts must be made by the

investigator to secure follow-up information (i.e., slit-lamp findings and general visual acuity, etc.) from the subject's new physician.

A subject will be considered a non-randomized screen failure if he/she does not meet the inclusion/exclusion criteria, if consent is withdrawn prior to randomization or death occurs prior to treatment.

A subject will be considered a randomized screen failure if the subject is randomized but does not undergo surgery or does not receive a study/control OVD for various reasons including: subject does not meet the inclusion/exclusion criteria, the planned implant was aborted due to surgical complications, the subject withdrew consent prior to treatment or the subject died prior to treatment. If a subject receives the study or control OVD in at least one eye, he/she is to be followed according to the protocol.

If a subject is exited early from the study, the investigator will complete an Exit Case Report Form in EDC indicating the reason for study exit. In the event of a lens removal or other serious adverse event, the subject may be exited from the study; however, efforts must be made by the investigator to follow the subject until resolution of the adverse event.

Following study completion or early exit, subjects may be informed about which OVD model they received. Additionally, all study subjects are to be instructed to undergo regular eye examinations at least yearly and also to return to their doctor if any eye complications are experienced in the interim.

[redacted]

10.10 UNSCHEDULED VISITS

During the study period, if a non-protocol-required visit is done for the purpose of medically-indicated follow-up for either study eye, data from this visit should be submitted using the Unscheduled Visit CRF. The need for unscheduled visits is at the investigator's discretion. Specific examinations to be performed at unscheduled visits are also at the discretion of the investigator (based on the reason for the unscheduled visit), and data are to be recorded in the appropriate section of the case report form.

Data to be collected may include:

- Uncorrected and best corrected distance visual acuity
- Manifest refraction
- Intraocular pressure
- Slit-lamp examination for medical and/or lens findings
- Dilated fundus exam
- Adverse events
- Ocular Medications

10.11 PROTOCOL DEVIATIONS

Any departure from the protocol procedures represents a protocol deviation. Protocol deviations may be subject-based (e.g., inclusion/exclusion criteria, informed consent deviation, etc.) or procedural-based (e.g., out-of-interval visits, non-compliance with testing procedures, etc.). All protocol deviations will be documented, and corrective actions will be implemented as appropriate. Any deviation made to protect the life or physical well-being of a subject in an emergency as well as any use of the investigational device without obtaining informed consent must be reported to JJSV within 5 working days. Protocol deviations will be monitored by JJSV, and if the non-compliance is persistent or egregious, JJSV may take action, including but not limited to termination of the investigator's participation in the study. The investigator is also responsible for informing the reviewing IRB of instances of protocol non-compliance in accordance with the IRB requirements. JJSV cannot grant permission to use waiver from the study protocol.

11. ADVERSE EVENTS AND PRODUCT COMPLAINTS

11.1 ADVERSE EVENT DEFINITIONS

Adverse Event (AE)

An adverse event is defined (following ISO 14155) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

Serious Adverse Event (SAE)

An adverse event is considered serious (following ISO 14155) if it is an untoward occurrence which may or may not be related to use of the study device that

- is sight- or life-threatening,
- results in death,
- requires inpatient hospitalization or prolongation of hospitalization (a planned hospitalization for a pre-existing condition without a serious deterioration in health is not considered a serious adverse event),
- results in permanent impairment of a body structure or body function including chronic diseases,
- necessitates medical or surgical intervention to prevent permanent impairment to a body structure or function, or
- results in fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Device-Related Adverse Event/Adverse Device Effect (ADE)

A device-related adverse event is defined as any adverse even that is believed to be definitely, probably or possibly related to the study device (following the guidelines in Section 11.4, Causal Relationship). A device-related event is also considered an adverse

device effect (ADE; following ISO 14155) resulting from the use of the study device that may result from user error, insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation of any malfunction of the device.

Study-Specific Serious Anticipated Adverse Events

The following is a list including, but not limited to, ocular adverse events that are anticipated and must be reported to JJSV for this study. Any events that are unlikely but anticipated (i.e., endophthalmitis) will be reported to the FDA and other appropriate regulatory agencies.

- Endophthalmitis/Intraocular infection
- Hypopyon
- Hyphema
- IOL dislocation
- Cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Persistent corneal edema
- Persistent iritis
- Raised IOP requiring treatment (i.e., IOP ≥ 30 mmHg)
- Visual symptoms requiring secondary surgical intervention (e.g., lens removal)
- Tilt and decentration requiring secondary surgical intervention (e.g., repositioning)
- Residual refractive error resulting in a secondary surgical intervention
- Retained lens material resulting in secondary surgical intervention

NOTE 1: Suture removal, planned blepharoplasty and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

NOTE 2: Corneal edema and iritis will only be considered serious if sight-threatening at the time of occurrence. Treatment merely to hasten the resolution of such conditions (and not intended to prevent permanent damage to the eye) will not be reported as serious adverse events.

NOTE 3: Corneal edema, and chronic anterior uveitis/iritis will be considered serious if corneal edema results in BCDVA of 20/40 or worse at 1 month or later; and Grade 1+ uveitis/iritis persists longer than 3 months.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE)

Any UADE (USA 21CFR 812.3(s)) or USADE (ISO 14155) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (i.e., this protocol), application (including a supplementary plan or application), or risk assessment, or any

other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Health Threat

A serious health threat (following ISO 14155) is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subject, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.2 PRODUCT COMPLAINT/DEVICE DEFICIENCY DEFINITION

A product complaint/device deficiency is defined (21 CFR 820.3(b) and ISO 14155) as any alleged deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device. This may include malfunctions, use error and inadequacies in labeling. Product complaints can pertain to any marketed JJSV device being used in the study as well as the investigational device. The investigator is to assess whether the deficiency could have led to a serious adverse event without suitable action or intervention or under less fortunate circumstances.

11.3 ADVERSE EVENT AND COMPLAINT REPORTING REQUIREMENTS

All adverse events and any complaint encountered using any JJSV product, regardless of severity and whether or not attributed to the study device(s), are to be reported to JJSV and recorded on the case report form corresponding to the visit during which awareness of the event occurred. Adverse events are also to be reported to the reviewing IRB as per the IRB reporting requirements. If required, adverse events will be reported to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations.

Reporting of adverse events shall follow the USA Code of Federal Regulations (21CFR812).

General guidelines are provided below:

Adverse Event Reporting

An adverse event that is not serious or device-related is to be reported to JJSV in a timely manner. Notification of non-serious and non-device related adverse events will occur by recording events on the CRF when noted. Such adverse events are also to be reported to the reviewing IRB per their reporting requirements.

Complaints/Device Deficiency Reporting

A general product complaint or device deficiency is to be reported to JJSV in a timely manner. Notification of complaints/device deficiencies will occur by either recording complaints on the CRF when the complaint occurred (e.g. operative form) or by a phone call to the Sponsor. Any device deficiency that could have led to a serious adverse event without suitable action or intervention, or under less fortunate circumstances, must be reported to the sponsor immediately (no later than 24 hours after detection). Device deficiencies that could have led to a serious adverse event should also be reported to the investigator's IRB per their reporting requirements.

Serious and/or Device-Related Adverse Event Reporting

Serious and/or device related events (ADEs) are to be documented using the Detailed Adverse Event CRF. In the event of a serious adverse event (SAE), which may or may not be related to use of the study device, JJSV must be notified immediately (no later than 48 hours after detection). Any SAE is to be reported by phone (and/or email) and by submitting the completed Detailed Adverse Event CRF. Any SAE or device-related AE should also be reported to the investigator's IRB/IEC per their reporting requirements.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE) Reporting

If during the study, a serious adverse event occurs that may reasonably be regarded as device-related and was not previously expected in nature, severity, or degree of incidence, the investigator is to report the UADE/USADE to JJSV immediately (no later than 48 hours after detection), and to the investigator's IRB as soon as possible (and no later than 10 working days after learning of the event for sites in the USA as required by 21CFR812).

11.4 CAUSAL RELATIONSHIP

The investigator should always be alert to adverse events that may be related to the study device or the use of the study device (i.e., the procedure specific to the initial application of the device). An attempt should be made in every case to determine the causality of the event. The following definitions are to be used as guidelines in determining the relationship between the event and the study device and/or use of the device.

Definitely related:	If the event is associated with the device and/or the use of the device beyond a reasonable doubt, a causal relationship exists between the adverse event and the device and/or the use of the study device.
Probably related:	There is a reasonable possibility of a causal relationship between the adverse event and the device and/or the use of the study

	device and/or the adverse event cannot be reasonably explained by another cause.
Possibly related:	The adverse event has not been determined to be related to the device or the use of the device, but no other cause has been identified and the device and/or the use of the study device cannot be ruled out as a possible cause.
Unlikely to be related:	The possibility of a potential causal relationship between adverse event and the device and/or the use of the device could exist, but the adverse event can be reasonably explained by another cause.
Not related:	There is no possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event can be attributed to another cause.

If an adverse event is believed to be definitely, probably or possibly related to the study device and/or the use of the device, the event will be considered related to the study device and/or the use of the device.

11.5 ADVERSE EVENT FOLLOW-UP

For every adverse event, appropriate measures should be undertaken to treat and/or monitor the subject until resolution occurs. Obtain and maintain in the subject's files all pertinent medical data relating to the event including the subject's medical records and medical reports and/or judgments from colleagues or outside specialists who assisted in the treatment and follow-up of the subject. The investigator should keep JJSV closely informed as to the outcome of serious and/or device-related adverse events, thereby allowing JJSV to comply with the appropriate regulatory reporting requirements. A Detailed Adverse Event Update CRF should be completed each time the subject returns to the investigator or other specialist(s) for follow-up of serious and/or device-related adverse event until resolution of the event. Any subject who is exited from the study due to a serious and/or device-related adverse event will be followed until the outcome is determined.

12. PROTOCOL CHANGES/AMENDMENTS

If the investigator desires to modify any procedure and/or the design of the study, he or she must contact and obtain consent from JJSV regarding the proposed changes prior to implementation. Any modifications (including additional data collection) require approval by the FDA and all other appropriate regulatory agencies, as well as approval of the governing IRB prior to implementation.

13. ETHICS REVIEW AND PATIENT WELFARE

13.1 INSTITUTIONAL REVIEW BOARD (IRB)

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV.

The investigator is responsible for notifying the IRB of reportable adverse events as well as any other circumstance in which additional procedures outside the protocol were conducted to eliminate apparent hazards to subjects.

13.2 INFORMED CONSENT

The informed consent document will be provided as a physical or electronic document to each study subject for review prior to consenting. If using the electronic document, the study subject will be given an electronic tablet with the preloaded IRB-approved study specific informed consent. The current version of the IRB-approved study informed consent must be signed by each study subject prior to any study-specific examinations being performed. The IRB approved informed consent is to be signed and dated by the subject as well as by the person who conducted the informed consent discussion. Consent will be documented with required signatures on the physical document or on the electronic document. The signed informed consent will be maintained by the investigator as a permanent part of the subject's medical records. A copy of the signed and dated form is to be provided to the subject. If the electronic document is used for consenting, study subjects can elect to receive either a printed or electronic copy of the informed consent documents. Signed and submitted informed consent documents will be available as PDFs in the electronic consent repository. The investigator will provide JJSV written acknowledgement on the preoperative case report form that a signed agreement of informed consent has been obtained and is in the investigator's possession for each subject. As required by 21CFR812 Part G, the site shall document in the source documents that informed consent was obtained prior to participation in the study for each subject enrolled.

NOTE: The informed consent process also includes obtaining the subject's signature on an Authorization for Use/Disclosure of Health Information for Research Form or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries.

NOTE: The sponsor will secure appropriate insurance for study subjects prior to study start.

14. DOCUMENTATION

14.1 SOURCE DOCUMENTS

Source documents must be kept for all study subjects. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as results of any diagnostic tests or procedures such as topographies or laboratory tests with photographs or instrument printouts.

Each site is expected to adhere to the clinic's own standard documentation requirements for medical charts/clinic notes. However, for the purposes of this clinical study, the medical charts/clinic notes must also include, at a minimum, the following data that will be considered source data and will be reviewed by JJSV:

- Subject's name and study identification number
- Subject's contact information
- Study protocol number and the Sponsor name (JJSV)
- A statement that informed consent was obtained prior to participation in the study (including the date)
- Evidence of subject eligibility
- Dates of all subject visits and surgeries throughout the duration of the study
- OVD serial number identification (NOTE: This is masked information, and may only be reviewed by unmasked study staff)
- Concurrent medications
- Corrected and uncorrected distance visual acuity
- IOP
- ECC
- Manifest refraction
- Occurrence and status of any operative complications, postoperative medical or lens findings and adverse events
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for early exit.

14.2 SUBJECT CONFIDENTIALITY

Subjects will be assigned a unique subject number at the time of enrollment as a means of identification on study documents. Subject confidentiality will be maintained by recording only the subject number on the CRFs. Subject names may possibly be disclosed to JJSV or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to protect and maintain confidentiality of personal information to the extent permitted by applicable laws and regulations.

14.3 CASE REPORT FORM COMPLETION

This study will use an electronic data capture system. All study staff responsible for entering data into the system must complete certification prior to using the system. The investigator is responsible for ensuring that data are properly recorded on each subject's case report forms and related documents. Prior to database lock, the investigator will verify completeness and accuracy of data submitted to JJSV.

[redacted]

15. MONITORING

JJSV will perform three types of monitoring to ensure compliance with regulations: data monitoring, administrative monitoring, and safety monitoring.

15.1 DATA MONITORING

In order to ensure a well-controlled clinical trial, JJSV will follow specific data monitoring procedures, routinely generate reports and periodically review safety and effectiveness data. To avoid bias, any analyses generated prior to site closures will not be disseminated to any of the investigative sites.

An electronic data capture (EDC) system will be used to transmit case report forms from the investigative site to JJSV. Requests for data clarification will be handled through this same system. To minimize data omissions and inconsistencies on clinical reports and to ensure that data are accurately transcribed to computer data files, JJSV will follow internal data processing procedures that include automated and manual quality control checks to identify any data discrepancies. Any such items will be resolved and documented as needed in the EDC system.

Prevention of Missing Data

Methods used to safeguard against missing data that can have deleterious effects on the study integrity and reliability of its outcomes will include training study staff -via online conferencing, centralized and/or on-site programs. In addition, subjects will be encouraged at the time of informed consent to avoid missing study visits, as missing data may affect the study reliability and diminish the scientific value of their contribution to the study.

15.2 ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that study devices, subjects, and forms can be traced and will allow monitoring of investigator progress and compliance.

Accountability and traceability of study devices will be monitored by trained JJSV personnel.

Study Device Accountability

Complete OVD accountability will be maintained at the investigative site by maintaining records of all investigational OVDs received from and returned to JJSV. A site log will be used to track OVDs for date of receipt, use and disposition/return to JJSV. This site log and any other OVD information will be maintained in the operative room study binder and monitored by JJSV personnel. During periodic site monitoring visits, JJSV personnel will review inventory records and logs to ensure OVD accountability compliance and complete OVD traceability.

Site Monitoring Plan

Prior to performing any study surgeries, the requirements of the study and reporting mechanisms will be explained to each investigator either personally at the investigative site or at a formal study investigator meeting. When necessary, a pre-study site qualification visit may be performed to assess the adequacy of the site to perform the study for sites that have not previously worked with JJSV or have undergone significant changes, or have not been visited in the past year. A study initiation visit will be conducted for all sites prior to or at the time of the first study surgery.

Throughout the duration of the study, site visits to monitor compliance to this protocol will be made at each investigative site. During a routine site monitoring visit, JJSV will review informed consent documents and subject eligibility, and the data on study case report forms will be verified against subject charts and other source documents to ensure complete and accurate reporting. The subject files will also be reviewed to assure that all adverse events and any issues encountered with JJSV products have been reported in a timely fashion.

JJSV will also review source documents to verify that all required items have been documented in the subject medical charts. Refer to Section 14.1, Source Documents, for a list of items that are required for source documentation Additionally, study logs will be checked to ensure compliance with study procedures.

Training on study-specific procedures may also be conducted during monitoring visits.

Upon study completion, a final close-out site visit to each site will be made to monitor the last of the subject data records and finalize any outstanding study issues.

A separate Study Monitoring Plan will be established prior to study start that will define the type and frequency of monitoring visits and frequency of record monitoring.

15.3 SAFETY MONITORING

The Medical Monitor will review and assess any reports of serious and/or device-related adverse events as well as device deficiencies that could have led to a serious adverse event. If necessary, the medical monitor will discuss these events with the reporting investigator(s), without being specific about OVD type. If unmasking is required by the Medical Monitor to protect the safety of the subject(s), a request will be submitted and approved by Head of Clinical Sciences and Head of Biostatistics prior to release of the randomization code for only the subject(s) involved and the IRB will be notified. The medical monitor will also be available to answer all questions from investigators. The medical monitor, as well as any other qualified personnel designated by JJSV, shall also review interim progress reports, as applicable.

The Safety Management Team (SMT) will evaluate participant safety data throughout the duration of the trial and provide recommendations to either continue, amend or terminate a clinical trial based on this information. The presence of unanticipated device effects (UADEs), observed events that raise concern or events highlighted through trending and signal detection are all reasons that the SMT might recommend escalation to Product Safety Council or additional safety reviews to assess the impact on the study's benefit/risk analysis and/or if appropriate corrective actions are warranted including possible early termination of the clinical trial. The individuals comprising the SMT and the frequency of SMT review is required to be documented in the Safety Management Plan.

16. RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

RISKS OF THE BACTERIALLY-DERIVED HEALON ENDOCOAT PRO OVD

The bacterially-derived Healon EndoCoat PRO OVD is intended for use in anterior segment ophthalmic surgical procedures of the human eye. Like the non-investigational, Healon EndoCoat OVD, the Healon EndoCoat PRO OVD is designed to create and maintain a deep anterior chamber which facilitates manipulation inside the eye with reduced trauma to the corneal endothelium and other ocular tissues. The Healon EndoCoat PRO OVD can also be used to efficiently separate and control ocular tissues. The Healon EndoCoat PRO OVD is not designed to have any pharmacological effect.

The potential for early and short-term postoperative intraocular pressure (IOP) spikes exists with dispersive OVDs, which potentially require more time and care to remove from the eye. Therefore, it is recommended that Healon EndoCoat PRO and Healon EndoCoat OVD be removed from the eye completely by irrigating and aspirating with sterile irrigation solution to reduce the risk of early postoperative IOP spikes. Due to the greater viscosity of the Healon EndoCoat PRO OVD, the effect in IOP may be higher with the Healon EndoCoat PRO OVD than if the same volume of other sodium hyaluronate viscoelastic

products, with lower zero-shear viscosity, is left in the anterior chamber of the eye. Long-term risks of IOP spikes include secondary glaucoma, visual field loss and optic nerve damage.

GENERAL RISKS OF CATARACT SURGERY AND IOL IMPLANTATION

There are risks and complications associated with cataract surgery and IOL implantation in general. These can include worsening of vision, hemorrhage, loss of corneal clarity, inflammation, infections, retinal detachment, pupil changes, glaucoma, etc. Complications can result in poor vision, loss of vision or loss of the eye.

RISK MANAGEMENT

Subjects will be closely monitored thought the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to JJSV according to Section 11.0, Adverse Events and Product Complaints. Additionally, JJSV will monitor incoming data following the procedures outlined in Section 15.0, Monitoring. The Medical Monitor will ensure subjects are not exposed to additional risks by monitoring serious adverse events, device-related adverse events, and device-deficiencies that could have led to serious adverse events (Section 15.3, Safety Monitoring).

POTENTIAL BENEFITS

The general clinical performance of the bacterially-derived Healon EndoCoat PRO OVD is expected to be the same as the currently available Healon EndoCoat OVD. Bacterially-derived Healon EndoCoat PRO is designed to create and maintain a deep anterior chamber, which facilitates manipulation inside the eye with reduced trauma to the corneal endothelium and other ocular tissues. It can also be used to efficiently separate and control ocular tissues.

CONCLUSION

The hazards/risks associated with the Healon EndoCoat PRO OVD are acceptable and within those of the currently available Healon EndoCoat OVD. The potential clinical benefits of the bacterially-derived Healon EndoCoat PRO outweigh the residual risks when the device is used as intended.

17. RECORD RETENTION

All study-related correspondence, subject records, consent forms, Authorization for Use/Disclosure of Health Information Forms or similar medical treatment privacy law documentation, records of the distribution and use of all study products, and a copy of the electronic case report forms should be maintained by the investigator.

The investigator must maintain and have access to the following essential documents until notified by the Sponsor. Note: This may be for a minimum of 15 years after completion

of the study unless country-specific requirements are longer. JJSV requires notification if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

- All case report forms
- All adverse event information (detailed adverse event forms, follow-up letters, etc.)
- Investigational supply records/inventory
- IRB and regulatory approval documentation
- Study correspondence
- Study agreements
- Site visit documentation
- Protocol(s) and the reason for any deviations from the protocol
- Subject log(s)
- Clinical Investigator's Brochure
- Completed subject informed consent forms and medical privacy forms (e.g., Authorization for Use/Disclosure of Health information or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries)
- Subject medical chart/clinic notes

18. TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event of high levels of complications and/or adverse events that are unexpected in nature and/or severity and evaluated as to causality relative to the study device. The clinical investigation may be suspended if the Medical Monitor or IRB, upon review and evaluation of the clinical data, finds unacceptable clinical performance or the level of single or total complications and/or adverse events unacceptable for continuation of the investigation.

If causality is shown not to be related to the study device, the study may be resumed in accordance with the IRB and regulations of the FDA and governing countries. The study will be terminated if causality is shown to be related to the study device.

Additionally, the investigator, or JJSV, may stop a subject's participation at any time. JJSV may also stop the study at any time for reasons it determines appropriate. However, no suspension of the study would be made to disadvantage the study subjects. Following suspension of the study for any reason, all study subjects who have already received treatment would continue to be followed through completion of the study visit schedule.

19. STATISTICAL METHODS

This section highlights the analyses for the primary and other key endpoints. The detailed plan for all analyses will be documented in the Statistical Analysis Plan (SAP). Data from the 3-month postoperative visit will be the key timeframe for the primary and key endpoints. The operative day visit is the key analysis time point for the user acceptance endpoint. Data from other study visits will be reported for supportive analysis. All complications and adverse events will be evaluated at all visits.

Summary statistics include mean, standard deviation, median, minimum, and maximum for continuous variables, and frequency counts and proportions for categorical endpoints. In addition to the point estimates, the appropriate 95% confidence interval may be calculated. All descriptive summaries will be presented by OVD. [redacted]

19.1 ANALYSIS POPULATION

- mITT: modified ITT population will consist of all randomized subjects who have any investigational or control OVD used. Subjects will be analyzed as per planned randomization schema.
- Safety: Safety Population (SP) will consist of all subjects who have any investigational or control OVD used or attempted use (defined as either OVD system coming into contact with the eye) and analyzed per treatment received.
- Per-Protocol: Per-Protocol Population will include subjects with an investigational or control OVD used, evaluated within the proper study interval and without clinically relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints) in both eyes as determined prior to database lock.
- [redacted]
- [redacted]

19.2 MISSING DATA HANDLING RULES

The primary analysis will be based on the multiple imputation approach for all primary endpoints. For assessing the impact of missing data on primary analyses of the primary safety (cumulative rate of IOP spike) and effectiveness (mean percent ECC change) endpoints, the following missing data handling rules will be applied.

[redacted]

The primary endpoints analyses based on observed case data (i.e., no imputation for missing values) will be used to supplement the inspection of the impact of missing data on the primary endpoints.

Full details regarding methods for the imputations will be outlined in the SAP.

19.3 STUDY ENDPOINTS

Primary Endpoints

The safety population will be the primary analysis set for the primary safety endpoint; the mITT population will be the primary analysis set for the primary effectiveness endpoint.

[redacted]

SAFETY: CUMULATIVE RATE OF IOP SPIKES 30 MMHG OR GREATER MEASURED POSTOPERATIVELY

The cumulative count and proportion of eyes with an IOP spike at 3 months will be reported by OVD groups. Cumulative IOP spikes are defined as an IOP of 30 mmHg or greater at any visit.

Hypothesis Testing

The null and alternative hypotheses for testing the non-inferiority of the test Healon EndoCoat PRO OVD compared to the control Healon EndoCoat OVD with respect to cumulative IOP spike rate at 3 months (p) are as follows:

$$H_0: p_{test-control} \geq \delta$$
$$H_A: p_{test-control} < \delta$$

[redacted]

Success Criteria: the upper bound of the 2-sided 95% confidence interval for $p_{test-control}$ is less than 10%.

[redacted]

[redacted]

EFFECTIVENESS: MEAN PERCENT ECC CHANGE PREOPERATIVELY VS. POSTOPERATIVELY

The percent change in ECC from preoperative to 3 months postoperative will be reported by descriptive statistics by OVD groups. The percent change in ECC from preoperative to postoperative is calculated as followed:

Percent change in ECC = [(Postop ECC minus Preop ECC)/Preop ECC] *100%

Hypothesis Testing

The null and alternative hypotheses for testing the non-inferiority of the test Healon EndoCoat PRO OVD compared to the control Healon EndoCoat OVD with respect to percent change in ECC at 3 months (μ) are as follows:

$$H_0: \mu_{test-control} \leq \delta$$
$$H_A: \mu_{test-control} > \delta$$

[redacted]

Success Criteria: the lower bound of the 2-sided 95% confidence interval for $\mu_{test-control}$ is greater than -5%.

[redacted]

[redacted]

SITE HETEROGENEITY AND OTHER COVARIATES

The analysis of site heterogeneity and of the potential impact of other key covariates [redacted] on the primary endpoints will be performed using the safety population observed case data for primary safety endpoint and using the mITT population observed case data for primary effectiveness endpoint.

[redacted]

Other Endpoints

The Safety population will be used for the analyses of all safety and other endpoints.

The percentage of IOP spikes at 8 hours, 1 day, 1 week, 1 month and 3 months postoperatively will be summarized by OVD and the corresponding 95% CI of the paired-eye difference in proportions will be presented. No adjustment in the confidence level for multiple CIs will be made. [redacted]

The change in IOP from preoperative will be presented by descriptive statistics for the 8-hour [redacted] 1-day, 1-week, 1-month and 3-month postoperative time points by OVD. The 8-hour visit will also be stratified in 2-hour intervals [redacted]

ECC for preoperative, 3 months postoperative and the difference between preoperative and 3 months will be summarized using descriptive statistics.

The grades of inflammation for epithelial and stromal edema, cells and flare, anterior and posterior synechiae, and fibrin presence will be tabulated with the count and proportion of eyes with each grading for each event over time and cumulatively will be presented descriptively for both OVDs.

Additional IOP, ECC and inflammation related analysis described in ISO/FDIS 15798:2021 Annex C will further be detailed in the statistical analysis plan.

All SPE types of adverse events reported in the test OVD will be compared to ISO SPE rates using a one-sided 95% Clopper Pearson exact confidence interval. The test AE rate is considered not significantly higher than ISO SPE rate if the lower limit of one-sided 95% confidence interval is less than the SPE rate.

The count and proportion of monocular BCDVA will be reported over time by visual acuity line. Percentage of eyes with monocular BCDVA 20/40 or better which received the test OVD will be compared to ISO SPE rate. The test BCDVA rate is considered not significantly lower than ISO SPE rate if the upper limit of one-sided 95% confidence interval is greater than the SPE rate.

The count and proportion of monocular UCDVA at 1 day will be reported by visual acuity line.

19.4 SAMPLE SIZE CALCULATIONS

[redacted]