Study Protocol

Title: Clinical Investigation of the Bacterially-Derived Healon5 Ophthalmic Viscosurgical Device (OVD)

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Clinical Investigation of the
Bacterially-Derived Healon5 Ophthalmic Viscosurgical Device (OVD)

PROTOCOL NUMBER: VSCO-109-HLN5

SPONSOR: Abbott Medical Optics Inc.
1700 E. St. Andrew Place
Santa Ana, CA 92705
714-247-8200

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) and FDA; 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 Abbott Medical Optics 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
Subinvestigator Printed Name	Signature	Date

Acknowledged By:

Signature of Sponsor's Representative	Date

Printed Name and Title

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PROTOCOL CHANGE HISTORY

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original	N/A
2.0	1.0, 6.2, 20.1, 20.2,	3, 6, 33-35	Study endpoints updated to move adverse events, inflammation, IOP spikes over time, and mean change in IOP from baseline from other endpoints to secondary safety endpoints.	To address FDA considerations in letter dated January 6, 2016
	6.0	6	Primary study endpoints specifically identified as safety or effectiveness.	
	10.2	13-14	Visit schedule updated to specify there will be at least 14 days between first and second eye surgery; one day visit will have a 24 hour window ±4 hours (20-28 hours)	
	10.5	16-17	Medications were standardized and IOP management medications are left to the investigator's choice for best patient care.	
	11.1	23	Note 2 regarding corneal edema and iritis as serious adverse events was updated for clarification.	
	17.0	31	Potential benefits updated for clarification.	
	19.0	32	Updated to clarify considerations for termination of investigation.	
3.0	10.5	16	Updated postoperative medications for clarification	To address FDA considerations in letter dated March 8, 2016
4.0	N/A, Appendix E	iv, 42	Updated study manager, emergency name and contact information	Due to study personnel changes
	1.0, 7.2, 9.1, and 10.6	1, 8, 10, 17	Updated IOL options to include the TECNIS Symfony IOL	Requested by study investigators due to recent FDA approval of the TECNIS Symfony IOL, which is part of the TECNIS 1-Piece family of IOLs already being used in the study.
	1.0, 5.0, 10.6	4, 6,17	Allow for Laser Cataract Surgery and AK or LRI	Clarifying that laser assisted cataract surgery and relaxing incisions are allowed

	10.5, 10.7, 11.3, 11.5, 18.0 and Appendix E	17, 19, 24, 25, 32, 42	Change the name of the SAE/ADE reporting form	To be consistent with the name of the form in the EDC system.
	Appendix B	38	Updated to include a refrigerator and sensor	Clarifying additional equipment the sites received
	Appendix C	39	Updated the process for exporting the ECC images to the reading center directly. The process for collecting and analyzing the images remains the same.	To be consistent with the reading center submission process (images are to be submitted directly to the reading center, not to AMO).

1. SYNOPSIS

PROTOCOL: Clinical Investigation of the Bacterially-Derived Healon5 Ophthalmic Viscosurgical Device (OVD)
Protocol Number: VSCO-109-HLN5

STUDY TREATMENTS: Investigational Product: Bacterially-derived Healon5

Control Product: Currently-available, animal-derived Healon5

STUDY OBJECTIVE: The purpose of this clinical trial is to evaluate the safety and effectiveness of the bacterially-derived Healon5.

CLINICAL HYPOTHESIS: The bacterially-derived Healon5 OVD will be statistically non-inferior to the currently-available animal-derived Healon5 OVD with regard to cumulative intraoperative pressure (IOP) spikes and endothelial cell count (ECC) change at 3 months postoperatively.

OVERALL STUDY DESIGN:

Structure: Prospective, multicenter, paired-eye, randomized, masked, clinical trial of the bacterially-derived Healon5 OVD versus the currently available Healon5 OVD control.

Number of sites: Up to 10 sites in the USA

Duration: 3 months

Administration: Surgeons will use the OVD as they normally would to perform standard, small-incision, cataract surgery and implant subjects with one of the following intraocular lenses (IOLs): TECNIS® ZCB00 monofocal IOL, TECNIS® Multifocal IOLs (ZKB00, ZLB00, or ZMB00) or the TECNIS® Symfony Extended Range of Vision IOL (ZXR00).

Visit Schedule: All subjects will undergo a minimum of 11 visits: Preoperative for both eyes; 1st eye operative; Postoperative for 1st eye at 6 hours, 1 day and 1 week; 2nd eye operative; Postoperative for 2nd eye at 6 hours, 1 day and 1 week; 1 month and 3 months postoperative for both eyes together.

STUDY POPULATION CHARACTERISTICS:

Condition: Bilateral cataracts with otherwise healthy eyes

Number of Subjects: Up to 241 subjects will be enrolled to ensure treatment of approximately 230 subjects in order to achieve approximately 200 evaluable subjects at 3 months

Each site should enroll approximately 20 subjects, and no site may enroll more than 25% (60 subjects) of the enrollment total.

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

- Minimum 22 years of age
- Cataracts for which extraction and posterior IOL implantation have been planned for 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 visual outcomes or increase risk to the subject
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery
- 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 or worse during the study
- 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
- Subjects with 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
- 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)
- 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 lowest value 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 45 days prior to preoperative visit in any other clinical trial

EVALUATION CRITERIA:

The purpose of this clinical study is to evaluate the safety and effectiveness of the non-animal-derived Healon5 OVD. The primary endpoints are cumulative rate of intraocular pressure (IOP) spikes of 30 mmHg or greater postoperatively and mean percent change of endothelial cell count (ECC) postoperatively vs preoperatively. The secondary safety endpoints are rates of serious and/or device-related adverse events, distribution of the grade of inflammation, IOP spikes of 30 mmHg or greater at 6 hours, 1 day, 1 week, 1 month and 3 months postoperatively, and mean change in IOP from baseline. Additional endpoints are other medical findings/adverse events (non-serious, non-device-related), monocular best corrected distance visual acuity (BCDVA) percent 20/40 or better vs. ISO SPE rates, optical/visual symptoms, and uncorrected distance visual acuity (UCDVA) at 1 day.

As this study is masked, an independent Data Safety Monitoring Board (DSMB) will monitor medical complications and adverse events that occur during the study.

DATA ANALYSIS:

For primary endpoints of cumulative IOP spike rate and mean percent ECC change, the primary analysis population will be an Intent-to-Treat (ITT) population. For missing data, data imputation will be performed using MCMC multiple imputation techniques[1]. The safety population (SP) will be used for secondary safety endpoints and other supportive endpoints. Per-protocol and sensitivity analyses (e.g., worst-case, best-case and tipping-point analyses) will also be provided for the primary endpoints.

For cumulative IOP spike rate, comparison between OVD groups will be performed using a 1-sided, McNemar test of non-inferiority at an alpha of 0.025 and a non-inferiority margin of 0.10 (10%). For mean percent ECC change, comparison between OVD Groups will be performed using a 1-sided, paired t-test of non-inferiority at an alpha of 0.025 and a non-inferiority margin of 5%. If percent ECC change does not meet normality assumption, a non-parametric test will be performed to evaluate the non-inferiority of mean percent ECC change.

STUDY VISITS AND PROCEDURES:

Inclusion and exclusion qualifications will be assessed at the preoperative visit according to the inclusion/exclusion criteria. The Informed Consent Document and Authorization for Use/Disclosure of Health Information form (HIPAA authorization) must be signed by

any patients who agree to participate in the study prior to undergoing any study-specific procedures. After determination that all inclusion/exclusion criteria have been met, enrolled subjects will be randomized in a 1:1 ratio. Subjects will receive the study OVD in one eye and the currently-available control OVD in the fellow eye. Subjects and study personnel will be masked for the duration of the study.

Key preoperative data include ocular health and history, visual acuities, manifest refraction, IOP, ECC, biomicroscopic slit-lamp findings, ocular symptoms and biometry. The operative visit will include standard procedures for cataract surgery and IOL implantation. All aspects of laser cataract surgery will be allowed as well as astigmatic keratotomy (AK) and Limbal Relaxing Incisions (LRI). If laser cataract surgery, AK or LRI is elected, it must be performed on both eyes of the subject.

A standardized medication regimen will be used preoperatively and intraoperatively (Section 10.5, Medication Regimen). Key postoperative data collection includes IOP, ECC, manifest refraction, visual acuity, visual symptoms, biomicroscopic slit-lamp findings, and adverse events.

As this study is masked, an independent Data Safety Monitoring Board (DSMB) will monitor adverse events that occur during the study.

2. BACKGROUND/INTRODUCTION

Viscoelastics 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.[2] The protection these materials provide result in reduced trauma to the cornea from inadvertent "touch" during intraocular surgery, therefore minimizing endothelial cell loss.[3]

Viscoelastics traditionally have been developed from sodium hyaluronate (NaHA) derived from rooster combs such as the currently-available Healon5. Due to concerns of cross-over contamination, animal-derived products have been losing favor in many parts of the world. The OVD under investigation is a bacterially-derived sodium hyaluronate version of the currently-available, animal-derived Healon5. This clinical study will evaluate safety and effectiveness of the bacterially-derived Healon5 OVD under normal-use conditions during the cataract surgical procedure.

3. CLINICAL HYPOTHESIS

This study will demonstrate that the bacterially-derived Healon5 has non-inferior rates of IOP spikes and mean percent endothelial cell change compared to that of the animal-derived Healon5. Rates of serious and device-related adverse events and adverse event rates associated with the bacterially-derived Healon5 group will not be statistically significantly higher than ISO SPE rates.

4. STUDY DESIGN

This study is a 3-month, prospective, multicenter, paired-eye, masked, randomized clinical investigation of the bacterially-derived Healon5 versus the currently-available, animal-derived Healon5 control.

The study will be conducted at up to 10 sites in the USA and will include approximately 230 treated subjects of up to 241 enrolled subjects. Subjects will be randomly assigned to receive the study OVD in one eye and the control OVD in the fellow eye.

JUSTIFICATION OF STUDY DESIGN

This study is being conducted for USA regulatory purposes; a randomized, paired-eye, masked study design was chosen to optimize comparison of IOP spike rates and ECC loss between the bacterially-derived Healon5 and the animal-derived Healon5 control, while minimizing the number of subjects and allowing for a more robust control than a unilateral design would provide.

5. ACRONYMS

The following acronyms are used throughout the document:

- OVD: ophthalmic viscosurgical device
- IOP: intraocular pressure
- ECC: endothelial cell count
- AK: astigmatic keratotomy
- LRI: limbal relaxing incisions
- UCDVA: uncorrected distance visual acuity
- BCDVA: best corrected distance visual acuity

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the safety and effectiveness of the bacterially-derived Healon5 OVD. All study endpoints will be evaluated through 3 months.

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 bacterially-derived Healon5 will be statistically non-inferior to those for control eyes using a non-inferiority margin of 10%.

EFFECTIVENESS: MEAN PERCENT ECC CHANGE PREOPERATIVELY VS. POSTOPERATIVLEY

- Success criteria: The mean percent ECC change for the bacterially-derived Healon5 will be statistically non-inferior to those for control eyes using a non-inferiority margin of 5%.

6.2 SECONDARY SAFETY ENDPOINTS

- Serious and/or device-related adverse events
- Distribution of the grade of inflammation
  - Epithelial and stromal edema
  - Cells and flare
  - Anterior and posterior synechiae
  - Fibrin presence
- IOP spikes 30 mmHg of greater at 6 hours, 1 day, 1 week, 1 month and 3 months
- Mean change in IOP from baseline

6.3 OTHER ENDPOINTS

- Other medical findings/adverse events (non-serious, non-device-related)

- Monocular BCDVA percent 20/40 or better vs. ISO SPE
- Optical/visual symptoms
- Monocular UCDVA at 1 day

7. STUDY PRODUCTS

7.1 OPHTHALMIC VISCOSURGICAL DEVICES

The two OVDs used in this study include the investigational, bacterially-derived Healon5 and the currently-available, animal-derived Healon5 control. Both are considered viscoadaptive viscoelastics.

Investigational Bacterially-Derived Healon5 OVD

The bacterially-derived Healon5 is a sterile, non-pyrogenic, viscoelastic preparation of a highly-purified, non-inflammatory, high-molecular-weight sodium hyaluronate derived from bacterial fermentation of *Streptococcus equi*, which gives the product its rheological properties. The bacterially-derived Healon5 OVD contains 2.3% (23 mg/mL) of sodium hyaluronate dissolved in physiological sodium chloride phosphate buffer (pH 6.8-7.6) and has an intrinsic viscosity of approximately 3.3-4.5 m^3/kg. The high-molecular-weight polymer is made up of repeating disaccharide units of N-acetylglucosamine and sodium glucuronate linked by β 1-3 and β 1-4 glycosidic bond.

Animal-Derived Healon5 Control OVD

The currently-available, animal-derived Healon5 is a sterile, non-pyrogenic, viscoelastic preparation of a highly-purified, non-inflammatory, high-molecular-weight sodium hyaluronate derived from avian tissues, which gives the product its rheological properties. The animal-derived Healon5 OVD contains 2.3% (23 mg/mL) of sodium hyaluronate dissolved in physiological sodium chloride phosphate buffer (pH 7.0-7.5) and has an intrinsic viscosity of approximately 3.5-4.7 m^3/kg. The high-molecular-weight polymer is made up of repeating disaccharide units of N-acetylglucosamine and sodium glucuronate linked by β 1-3 and β 1-4 glycosidic bond.

INDICATIONS

Both the bacterial- and animal-derived Healon5 OVDs are intended for use in anterior segment ophthalmic surgical procedures of the human eye. Both Healon5 OVDs are 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. Both Healon5 OVDs can also be used to efficiently separate and control ocular tissues. Neither Healon5 OVDs are designed to have any pharmalogical effect.

STORAGE AND DISTRIBUTION

A consignment of both the investigational, bacterially-derived Healon5 and the currently-available, animal-derived Healon5 control will be supplied to the sites. Both OVD products must be stored between 2° to 8° C (36° to 46° F) in the temperature-controlled refrigerator provided by AMO. The OVDs should be protected from freezing and exposure to light. Refrigerated OVD should be held at room temperature for approximately 30 minutes before use. Both the investigational and control OVDs are supplied in 0.6 mL glass syringes. The syringes are terminally steam sterilized and aseptically packaged. A sterile, single-use 25 gauge cannula is included with each syringe. The OVDs are sterile as long as the package has not been opened or damaged and the shelf-life expiration date has not been exceeded. The Principal Investigator is responsible for ensuring that both OVD products provided are only used for subjects enrolled in this study.

7.2 IOLS AND IMPLANTATION SYSTEMS

In this study, only the following IOLs will be implanted: TECNIS® 1-Piece Monofocal Model PCB00 (preloaded), TECNIS® 1-Piece Monofocal Model ZCB00, TECNIS® 1-Piece Multifocal IOL Models ZKB00, ZLB00 and ZMB00 or the TECNIS® Symfony Extended Range of Vision IOL Model ZXR00. The TECNIS® 1-Piece Models ZCB00, ZKB00, ZLB00, ZMB00 and ZXR00 are to be implanted using the UNFOLDER Platinum 1 Series Implantation System (DK7796 handpiece with the UNFOLDER Platinum 1 Series cartridge, Model 1MTEC30) or the ONE SERIES Ultra Implantation System (DK7786 or DK7791 handpiece with the One Series Ultra cartridge). Another insertion system may be used for the lenses if validated by AMO prior to study use.

8. STUDY POPULATION

All study subjects will be enrolled from the normal surgical cataract population at up to 10 sites in the USA. Up to 241 subjects will be enrolled to achieve approximately 230 randomized and contralaterally-operated subjects to ensure approximately 200 evaluable subjects at 3 months. Each site should implant a minimum of 20 subjects, and no site may implant more than 25% of the enrollment total.

This study will include only subjects undergoing bilateral, primary, cataract extraction and IOL implantation and who meet all of the study inclusion and exclusion criteria in both eyes. All subjects who meet the inclusion/exclusion criteria will be offered enrollment in the study. Eligibility criteria may not be waived by the investigator. Any questions regarding patient eligibility are to be discussed with AMO prior to subject enrollment. Those subjects who meet the inclusion/exclusion criteria and agree to participate will be randomly assigned to receive the investigational OVD in one eye and

the currently-available, control OVD in the fellow eye. Subjects will be enrolled at each site sequentially until the recruitment goals are met or the site limit is reached.

8.1 INCLUSION CRITERIA

Note: All criteria apply to each eye

- Minimum 22 years of age
- Cataracts for which extraction and posterior IOL implantation have been planned for 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

Note: All criteria apply to each 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 visual outcomes or increase risk to the subject
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery
- 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
- 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.
- 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
- 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)
- 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 lowest value 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 45 days prior to preoperative visit, in any other clinical trial

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

AMO 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. Each site will have one designated principal investigator; some sites may have additional sub-investigators performing surgery for study cases.

Investigators will be selected from surgeons who are experienced in small-incision, cataract extraction and monofocal and/or multifocal IOL implantation in cataract patients. It is recommended that each investigator use his/her established personalized A-constant for the TECNIS Monofocal Model ZCB00, TECNIS Extended Range of Vision Model ZXR00 and/or TECNIS Multifocal Models ZKB00, ZLB00, ZMB00. 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 AMO, the FDA or other governing agencies, and the Institutional 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 AMO 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 AMO, duly-authorized regulatory agencies (e.g., FDA) and/or the IRB.
- Submit progress reports on the investigation to AMO 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 AMO.
- 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 AMO's request, return to AMO any remaining supply of the investigational device.
- Provide sufficient accurate financial information to AMO to allow AMO 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 and the FDA.
- 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 AMO of any change in the conduct of the study including changes in study personnel assigned to the study project, location of the investigational products(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 at the site. Copies of IRB submissions and approvals should be forwarded to AMO. Study sites will obtain IRB approvals and fulfill any other site-specific requirements. The investigator is required to report to AMO 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 AMO:

- 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.

10. EXPERIMENTAL PLAN

10.1 OVERVIEW

This study will be conducted in accordance with U.S. Code of Federal Regulations, the Declaration of Helsinki, ISO 14155 and all other applicable laws and regulations. The study will not begin until regulatory and IRB approvals have been obtained.

This study will be a prospective, multicenter, paired-eye, randomized, and masked clinical investigation conducted at up to 10 sites. Up to 241 subjects will be enrolled to achieve approximately 230 randomized and contralaterally-operated subjects to ensure approximately 200 evaluable subjects at 3 months. After informed consent is obtained and confirmation that all inclusion/exclusion criteria are met, the eye(s) may be randomized.

After signing the informed consent, subjects meeting all inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to receive either the bacterially-derived Healon5 or the animal-derived Healon5 control for the first-eye surgery and the other study product for the second-eye surgery. Prior to randomization for each subject, the investigator will choose which eye to operate on first based on his/her standard clinical practice (e.g., the eye with the worse cataract, poorer best corrected distance vision and/or more severe optical/visual complaints). All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week postoperative exam for the first eye, but no more than 45 days after the first-eye surgery. All subjects will be examined through 3 months postoperatively according to the visit schedule described in Section 10.2, Visit Schedule.

An independent Data Safety Monitoring Board (DSMB) will monitor complications and adverse events that occur during the study.

Key data collection for all subjects includes IOP, ECC, manifest refraction, visual acuities, biomicroscopic slit-lamp findings, complications and adverse events. A chart summary of all examination procedures required at each study visit is provided in **Appendix A**. If needed, specific equipment necessary to perform the required procedures will be supplied for the duration of the study (**Appendix B**).

10.2 VISIT SCHEDULE

The study visit schedule for all study subjects is outlined in **Table 1**.

All subjects enrolled are intended to have bilateral cataract surgery with the second-eye surgery occurring 14-45 days after the first-eye surgery (and after the 1 week exam for the first eye). After each surgery, each eye will be examined at 6 hours (4-8 hours) postoperatively, 1 day (20-28 hours) and again at 1 week (7-14 days). Additionally, following the second-eye surgery, both eyes will be evaluated at 1 month (23-37 days) and 3 months (75-105 days). Unscheduled visits may be conducted as necessary at the discretion of the investigator for medically-indicated follow-up.

TABLE 1: Visit Schedule

VISIT	EYES EVALUATED	EXAM	VISIT WINDOW
1	Both Eyes	Preoperative Exam	Within 45 days prior to 1st surgery
2	First Eye	Operative	0-45 days after preoperative exam
3	First Eye	6 hours	4-8 hours postoperative
4	First Eye	1 day	20-28 hours postoperative
5	First Eye	1 week[a]	7-14 days postoperative
6	Second Eye	Operative[a]	14-45 days after 1st eye surgery
7	Second Eye	6 hours	4-8 hours postoperative
8	Second Eye	1 day	20-28 hours postoperative
9	Second Eye	1 week	7-14 days postoperative
10	Both Eyes	1 month	23-37 days postoperative from 2nd implant
11	Both Eyes	3 months	75-105 days postoperative from 2nd implant

[a] The 1-week exam for the first eye must be completed prior to surgery on the second eye.

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. An Authorization for Use/Disclosure of Health Information Form (HIPAA authorization) must also be signed.

All preoperative testing for the study must be completed within 45 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 45 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 randomized and scheduled for surgery.

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 if they qualify but decide not to proceed with surgery. These subjects will be exited from the study.

Preoperative testing to be performed for each eye includes the following:

POTENTIAL DISTANCE VISUAL ACUITY

The subject must be capable of achieving Snellen 20/40 or better best corrected distance vision in each eye after cataract extraction and IOL implantation. The surgeon may use his/her judgment, the Potential Acuity Meter (PAM), or other methods (e.g., pinhole, laser interferometer, etc.) to estimate the subject's potential postoperative acuity.

INTRAOCULAR PRESSURE (IOP)

Preoperative IOP cannot be ≥ 20 mmHg. Additionally, medically-controlled ocular hypertension and/or glaucomatous changes in the optic nerve are exclusionary.

ENDOTHELIAL CELL COUNT (ECC)

Subject must have an ECC of at least 1800 cells/mm^2 to be enrolled. Three separate images will be taken of each eye and the lowest value of the three counts, as calculated by the Konan Specular Microscope, will be recorded. Note that ECC inclusion/exclusion criteria will be determined by the site; however, ECC images will be additionally analyzed by a centralized reading center for study endpoint analyses. Further instructions are provided in **Appendix C**.

ADDITIONAL PREOPERATIVE INFORMATION TO BE COLLECTED:

- Informed consent documentation
- Subject demographic information
- Determination of the first eye to be operated on and planned surgery dates for each eye
- Ocular history, including presence of ocular pathology for each eye
- Snellen BCDVA for each eye
- Ocular and systemic medications

10.4 RANDOMIZATION AND MASKING

A randomization list will be created by the AMO biostatistician for each investigative site. Subjects will be randomly assigned to receive either the bacterially-derived Healon5 or the animal-derived Healon5 control in the first operative eye on a 1:1 basis; subjects will then receive the OVD not used in the first-eye surgery in the fellow eye. The randomization codes will be uploaded into the electronic data capture system (EDC). 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, masked study and the differences between the two OVDs.

In order to ensure masking of all study personnel, both the investigational and control OVDs will be packaged the same in white boxes labeled “Investigational Device”.

10.5 STUDY MEDICATIONS AND IOP MANAGEMENT

Medications should be used as indicated below to minimize variation in treatment. Each investigator must be consistent with his/her medication regimen for each eye enrolled in the study. All preoperative, intraoperative, and postoperative medications must be recorded on the subject source documents. Routine use of intraocular anti-hypertensive medication and miotics is not permitted.

3 Days Preoperative:

Standard medication regimen, however:

- No steroids
- Ketorolac tromethamine (0.45% or 0.5%) 1 gtt bid

Operative:

Standard intraoperative regimen, **however:**

- No steroids
- At completion of case, topical antibiotic, anti-inflammatory and steroid permissible
- **No routine injection of antibiotics and/or steroids at close of procedure**

Postoperative:

- Prednisolone acetate and ketorolac tromethamine (0.45% or 0.5%):
  1gtt each qid x 1 week (first week postop)
  1gtt each tid x 1 week (second week postop)
  1gtt each bid x 1 week (third week postop)
  1gtt each qd x 1 week (fourth week postop)
- NO IOP-reducing medications are to be given, and no IOP-reducing interventions are to be done unless IOP is ≥ 30 mm Hg
- Other medications, aside from IOP-reducing medications and anti-inflammatories, may be given per the investigator’s standard medication regimen

IOP Management: **(**at any postoperative visit)

IOP < 30 mm Hg: No treatment

IOP ≥ 30 mm Hg: **(Complete an SAE/ADE Detailed Page; Section 11)**

- IOP-reducing medications are to be administered per the investigator's standard of care

The administration, at any time, of IOP-reducing drugs shall be documented, and the data from those subjects will be analyzed separately. If a subject's IOP remains elevated at 30 mm Hg or greater for longer than 24 hours, additional measurements must be made every 24 hours until the IOP returns below 30 mmHg.

10.6 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. At a minimum, the viscoelastic should be used to inflate the anterior chamber and coat the endothelium prior to cataract extraction and for IOL insertion. All investigators are to completely remove the OVD prior to the completion of each case using irrigation/aspiration (I/A). All subjects must be implanted with either a TECNIS 1-Piece Monofocal IOL (Model ZCB00 or PCB00), TECNIS 1-Piece Multifocal IOL (Model ZKB00, ZLB00 or ZMB00), or the TECNIS Symfony Extended Range of Vision IOL (Model ZXR00) for this study. Lenses should be inserted into the capsular bag using the UNFOLDER Platinum 1 Series Implantation System (DK7796 handpiece with the UNFOLDER Platinum 1 Series cartridge, Model 1MTEC30) or the ONE SERIES Ultra Implantation System (DK7786 or DK7791 handpiece with the One Series Ultra cartridge).

Standardization of surgical technique across all study sites is important in reducing outcome variability. Therefore, all sites are to adhere to the following technique unless operative complications require otherwise.

- Operative medications in accordance with Section 10.5
- Investigator's routine, small-incision, cataract extraction
- Laser assisted cataract surgery and AK or LRI will be allowed bilaterally.
- Implantation of TECNIS IOL Models ZCB00, PCB00, ZKB00, ZLB00, ZMB00 or ZXR00
- Optic/haptics placed in capsular bag
- Sutureless incision closure

Operative case report forms will include the following information:

LENS REMOVAL

Lens removal may occur using phacoemulsification only or through laser fragmentation and phacoemulsification/aspiration.

SURGICAL COMPLICATIONS

Should a surgical complication occur in either the first or second eye, implantation of a study lens will be at the investigator's discretion. However, in the event of capsular bag or zonular rupture, the TECNIS IOL should not be implanted if the complication may result in lens instability. Additionally, the lens is not to be implanted in the sulcus. In this case, the investigator may implant his/her choice of a back-up, non-investigational IOL. The subject will be followed per the protocol, although data may be analyzed separately.

MEDICATIONS

Medications not to be used preoperatively and intraoperatively are detailed in Section 10.5, Study Medications and IOP Management. All efforts should be made to follow the regimen described. Any changes or additions to the medications used will be considered a protocol deviation.

ADDITIONAL OPERATIVE INFORMATION TO BE COLLECTED INCLUDES:

- Date of surgery
- Operative eye
- Lens model, power and serial number
- Other surgical procedures
- Surgical technique according to protocol

10.7 POSTOPERATIVE PROCEDURES

Postoperatively, subjects will be examined according to the schedule in Section 10.2, Visit Schedule. Only the most recently operated eye will be evaluated at the 6-hour, 1-day and 1-week visits. Both eyes will be evaluated at the 1-month and 3-month visits.

To maintain consistency throughout the study, it is recommended that a single individual (study technician or coordinator designated by the investigator) conduct all postoperative study-related testing. In addition, a back-up person should also be designated and trained. The biomicroscopic slit-lamp exam, however, should be performed by the investigator or other qualified designee.

Note: Subjects are not to wear contact lenses postoperatively until after completion of this study. Wearing contact lenses may potentially cause corneal edema or topography changes that may influence the visual acuity results. During the study, if correction is required, spectacles should be prescribed.

The postoperative case report form will include the following information, although not all are required at every visit (See **Appendix A**):

DISTANCE VISUAL ACUITY TESTING

Snellen monocular UCDVA and BCDVA will be measured for all subjects postoperatively under photopic lighting conditions. For eyes unable to achieve a postoperative BCDVA of Snellen 20/40, a reason must be specified.

IOP

IOP will be measured at each postoperative visit by Goldmann applanation. Any IOP measurements of 30 mmHg or greater are to be considered a "spike". An SAE/ADE Detailed Page must be completed; spikes are to be managed as described in Section 10.5, Study Medications and IOP Management.

ECC

All endothelial cell counts will be performed with a Konan non-contact specular microscope preoperatively and at three months postoperatively. Three photos will be taken at each exam and electronic or paper copies sent to AMO. Further instructions are provided in **Appendix C**.

BIOMICROSCOPIC SLIT-LAMP EXAM

A biomicroscopic slit-lamp exam must be performed at each postoperative visit to determine the presence or absence of any medical or lens findings, complications or adverse events.

Findings of aqueous cells and flare, corneal edema, synechia and fibrin are to be rated using standardized grading scales of 0 to +4 (0 = none, +4 = severe) during the slit-lamp biomicroscopy. The specific grading scales are provided in **Appendix D**.

DILATED FUNDUS EXAM

A dilated fundus exam is to be performed only if medically indicated.

OCULAR SYMPTOMS (NON-DIRECTED; SPONTANEOUS)

Subjective ocular symptoms are to be assessed at each postoperative visit by asking "Are you having any difficulties with your eyes/vision?" Subjects should not be prompted for specific responses; however, if a subject reports halos, night glare or starbursts, the level of severity should be determined (mild, moderate or severe).

MEDICATIONS

Postoperative medications should be used as described in Section 10.5, Study Medications and IOP Management. Every attempt should be made to adhere to the regimen. Any changes or additions to the medications prescribed will be considered a protocol deviation. Medications will be recorded on each postoperative case report form as applicable.

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. See Section 11.0, Adverse Events, and **Appendix E,** Adverse Event Reporting Instructions, for further information.

10.8 EXIT OF SUBJECTS

An Exit Case Report Form will be submitted 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 AMO 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.

If a subject dies prior to study completion, he/she will be documented as discontinued from the study along with the reason for death. Subjects will be considered "lost-to-follow-up" from the study only if irretrievably lost for unavoidable reasons such as: subject moved/unable to locate, subject uncooperative/refuses further study participation, subject ill/unable to travel. In the event of subject relocation, efforts must be made by the investigator to secure follow-up information (i.e., IOP, 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 or if consent is withdrawn prior to randomization.

A subject will be considered a randomized screen failure if the subject is randomized but does not undergo surgery or receive one of the study OVDs for various reasons including: the surgery being aborted, the subject withdrawing consent prior to treatment or the subject dying prior to treatment. If a subject receives the study OVDs in either eye, he/she is to be followed according to the protocol.

If a subject is exited early from the study, the investigator will submit an Exit Case Report Form indicating the reason for study exit. In the event of a 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 will be informed about which OVD was used in each eye. Additionally, all study subjects are to be instructed to undergo regular eye examinations at least yearly and to return to their doctor if any eye complications are experienced in the interim.

10.9 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
- Intraocular pressure
- Slit-lamp examination for medical and/or lens findings
- Dilated fundus exam
- Ocular symptoms
- Adverse events
- Medications

10.10 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 using protocol deviation case report forms. 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 AMO within 5 working days. Protocol deviations will be monitored by AMO, and if the non-compliance is persistent or egregious, AMO 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.

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,
- 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

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

A device-related adverse event is defined as any adverse event 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 or 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 AMO for this study. Any events that are unlikely but anticipated (i.e., endophthalmitis) will be reported to the FDA.

- Endophthalmitis/Intraocular infection
- Hypopyon
- Hyphema
- IOL dislocation
- IOP 30 mmHg or greater at any time or persistent IOP of any level requiring treatment
- Cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Persistent corneal edema
- Persistent iritis
- 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 be reported as serious adverse events if sight-threatening at any time or persistent at the final study visit (75-105 days postoperative). 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.

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.

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, user error and inadequacies in labeling. Product complaints can pertain to any marketed AMO 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 AMO product, regardless of severity and whether or not attributed to the study device(s), are to be reported to AMO and submitted 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's reporting requirements. If required, adverse events will be reported to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations. Specific instructions on notification procedures to AMO are included in **Appendix E**, Adverse Event Reporting.

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 AMO in a timely manner. Notification of non-serious and non-device-related adverse events will occur by submitting 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 AMO in a timely manner. Notification of complaints/device deficiencies will occur by either submitting 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 48 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 SAE/ADE Detailed Page . In the event of a serious adverse event (SAE), which may or may not be related to use of the study device, AMO 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 a completed SAE/ADE Detailed Page. Any SAE or device-related AE should also be reported to the investigator's IRB 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 AMO within 48 hours, 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 AMO closely informed as to the outcome of serious and/or device-related adverse events, thereby allowing AMO to comply with the appropriate regulatory reporting requirements. A SAE/ADE Resolution Form should be submitted each time the subject returns to the investigator or other specialist(s) for follow-up of a 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 AMO regarding the proposed changes prior to

implementation. Any modifications (including additional data collection) require approval by the FDA as well as approval of the governing IRBs 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 at the site. Copies of IRB submissions and approvals should be forwarded to AMO.

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 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. 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. The investigator will provide AMO 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.

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 AMO:

- Subject's name and study identification number
- Subject's contact information.
- Study protocol number and the Sponsor name (AMO)A statement that informed consent was obtained prior to participation in the study (including the date)
- Dates of all subject visits and surgeries throughout the duration of the study
- Implant serial number identification
- Concurrent medications
- Corrected and uncorrected distance visual acuity
- IOP
- ECC
- Manifest refraction
- Occurrence and status of any operative complications, postoperative medical findings and adverse events
- Occurrence and status of any subject complaints, e.g., ocular/visual symptoms
- 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 site/subject number to maintain subject confidentiality. Subject names may possibly be disclosed to AMO or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to 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 closure, the investigator will verify completeness and accuracy of all data collected.

14.4 STUDY SUMMARY

A final investigator's summary will be provided to AMO and the reviewing IRB within 3 months after termination or the completion of the study or the investigator's part of the investigation.

15. MONITORING

AMO 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, AMO will follow specific data monitoring procedures. As this study is masked, any necessary review of safety and effectiveness data by OVD type will be done only by the Data Safety Monitoring Board (Section 15.3) until the final study visits are completed. Study staff and AMO personnel will remain masked until the final study visits have been completed.

An electronic data capture system (EDC) will be used to transmit case report forms from the investigative site to AMO. 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, AMO 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 on the case report forms at the investigative site and in the data management system at AMO.

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 with WebEx and 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 OVDs, subjects, and forms can be traced and will allow monitoring of investigator progress and compliance. Accountability and traceability of study OVDs will be monitored by AMO personnel.

Device Accountability

Complete OVD accountability will be maintained at the investigative site by maintaining records of all OVDs received from and returned to AMO. A site log will be used to track OVDs for date of receipt, use and disposition/return to AMO. This site log and any other OVD information will be maintained in the operative room study binder and monitored by AMO personnel. During periodic site monitoring visits, AMO 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 AMO 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 site. During a routine site monitoring visit, AMO 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 AMO products have been reported in a timely fashion.

AMO 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. 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

This study will use a Data Safety Monitoring Board (DSMB) for safety monitoring. In alignment with ISO 14155:2011(E), the DSMB is an independent committee that is established by AMO to assess, at intervals, the progress of the clinical investigation, the safety data, or the critical performance endpoints, and to recommend to the sponsor whether to continue, suspend, or stop the clinical investigation. The DSMB will have access to the randomization code to be able to assess safety by OVD group if required. The responsibilities of the DSMB will be detailed in a separate written procedure to establish the frequency of meetings, handling of emergency situations and documentation of such meetings.

This study will also utilize a Medical Monitor for safety monitoring. The Medical Monitor will remain masked until the final study visits have been completed. 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 Research 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 AMO, shall also review interim progress reports, as applicable.

16. PUBLICATIONS

Refer to the Clinical Trial Agreement for information regarding AMO publication policies.

17. RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

RISKS OF THE BACTERIALLY-DERIVED HEALON5 OVD

The bacterially-derived Healon5 OVD is intended for use in anterior segment ophthalmic surgical procedures of the human eye. Like the non-investigational, animal-derived Healon5 OVD, the bacterially-derived Healon5 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 Healon5 OVD can also be used to efficiently separate and control ocular tissues. The Healon5 OVD is not designed to have any pharmacological effect.

Complete removal of the Healon5 OVD (both bacterial-and animal-derived) is important to avoid intraocular pressure peaks (or spikes) postoperatively. Due to the greater concentration of sodium hyaluronate in the Healon5 OVD, the rise in IOP may be higher with the Healon5 OVD (either bacterial-or animal-derived) than if the same volume of other sodium hyaluronate viscoelastic products, with lower zero-sheer 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 throughout the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to AMO according to Section 11.0, Adverse Events and Product Complaints. Additionally, AMO will monitor incoming data following the procedures outlined in Section 15.0, Monitoring. Both the DSMB and 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 Healon5 OVD is expected to be the same as the currently-available, animal-derived Healon5; however, without the concerns of cross-over contamination. Bacterially-derived Healon5 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 bacterially-derived Healon5 are acceptable and within those of the currently-available, animal-derived Healon5. The potential clinical benefits of the bacterially-derived Healon5 outweigh the residual risks when the device is used as intended.

18. RECORDS RETENTION

All study-related correspondence, subject records, consent forms, Authorization for Use/Disclosure of Health Information Forms, records of the distribution and use of all study products, and EDC 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. AMO 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 within the EDC system
- All adverse event information (SAE/ADE Detailed pages, 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)
- Subject medical chart/clinic notes

19. 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 DSMB, 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 (such as if any subject has an IOP ≥ 30 mmHg at one week postoperatively or later).

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. The study will be terminated if causality is shown to be related to the study device.

Additionally, the investigator, or AMO, may stop a subject's participation at any time. AMO 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.

20. STATISTICAL METHODS

This section highlights the analyses for the primary study endpoint and for other key endpoints. The 3-month postoperative visit is the critical analysis time point for all endpoints unless stated otherwise.

20.1 ANALYSIS POPULATION

For the primary endpoints of cumulative IOP rate and mean percent ECC change, the primary analysis population will be an Intent-to-Treat (ITT) population. The ITT population will include all subjects who were randomized and had surgeries using a test OVD in one eye and a control OVD in the other eye. For randomized subjects who received study OVDs but did not have data available at a specific postoperative visit

(i.e., missing postoperative data), data imputation will be performed using MCMC multiple imputation techniques[1]. Per-protocol and sensitivity analyses (e.g., worst-case, best-case and tipping-point analysis) will also be provided for the primary IOP and ECC endpoints. Sensitivity analyses will include all randomized subjects whether a study OVD was used or not. The safety population (SP) will include available subjects who had one or both study OVDs with available data at the time of analysis (i.e., no data imputation). Only the safety population will be used for analyses of secondary safety endpoints and other endpoints. For the secondary safety endpoints, no multiplicity or imputation will be done since they are considered safety endpoints and are not intended for claims. Only safety population (SP) will be used for the secondary safety endpoints.

20.2 STUDY ENDPOINTS

Primary Endpoints

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

The cumulative frequency and proportion of eyes with an IOP spike will be reported for both OVD groups for safety population, PP population and sensitivity analysis. For ITT (with data imputation), only the difference between the OVD groups will be reported. The difference in the cumulative IOP spike rate will be analyzed by the McNemar test using a GLIMMIX procedure taking into account the paired data. The GLIMMIX model will model spike as the dependent variable and OVD group as an independent variable and include the SUBJECT = option for the paired eye data. The hypothesis testing of non-inferiority for cumulative percentage of IOP spikes will be tested using a 1-sided, McNemar test at an alpha of 0.025 with a delta of 0.10 (10%). The null hypothesis is that the paired difference between eyes is less than or equal to -10%. The alternative hypothesis is that the paired difference between eyes is greater than -10%.

H_o: $p_c - p_t \leq \delta$
H_a: $p_c - p_t > \delta$
where…
p_t = Test rate of IOP spikes 30 mm Hg or greater
p_c = Control rate of IOP spikes 30 mm Hg or greater
δ = non-inferiority margin: -10%

Success Criteria: If the lower 2-sided 95% confidence interval (equivalent to the 1-sided 97.5% CI) for the difference between the proportions is greater than -10% [2].

EFFECTIVENESS: MEAN PERCENT ECC CHANGE PREOPERATIVLEY VS. POSTOPERATIVELY

The mean percent change in ECC from preoperative to 3 months postoperative will be reported by descriptive statistics for both OVD groups for safety population, PP

population and sensitivity analysis. For ITT (with data imputation), only the mean difference between the two OVD groups will be reported. The percent change in ECC from preoperative to postoperative is calculated as followed:

Percent change in ECC = (Postop ECC minus Preop ECC)/Preop ECC

The difference in mean percent change in ECC will be analyzed by a paired t-test. The hypothesis testing of non-inferiority for mean percent ECC change will be tested using a 1-sided, paired t-test at an alpha of 0.025 and a delta of 5%. The null hypothesis is that the paired mean difference for mean percent change in ECC is equal to or less than -5%. The alternative hypothesis is that the paired mean difference in percent change between eyes is greater than -5%.

H_o: $\mu_{test} - \mu_{control} \leq \delta$

H_a: $\mu_{test} - \mu_{control} > \delta$

where…

μ_{test} = ECC percent change in test OVD

$\mu_{control}$ = ECC percent change in control OVD

δ = non-inferiority margin: -5%

Success Criteria: If the lower 2-sided 95% confidence interval (equivalent to 1-sided 97.5% CI) for the mean difference between eyes in percent change for ECC is greater than -5%.

If the distribution of the percent ECC change does not meet the normality assumption, a non-parametric test will be performed to evaluate the non-inferiority of ECC endpoint. A similar alpha level of 0.025 and a delta of 5% will be used for the 1-sided non-parametric test.

In addition, ECC for preoperative, 3 months postoperative and the difference between preoperative and 3 months will also be reported as supportive data using the safety population.

Secondary Safety Endpoints

Serious and/or device-related adverse events will be tabulated with the frequency and proportion of eyes with these events reported over time for both OVD groups. The adverse event rates will be compared to the ISO SPE rates. Comparison of the ISO SPE rates will be performed using an exact test based on the binomial distribution. The null hypothesis is that the study rate for test OVD is equal or lower than the ISO SPE rate, and the alternative hypothesis is that the study rate for test OVD is greater than the ISO SPE rate.

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

For the percentage of IOP spikes at 6 hours, 1 day, 1 week, 1 month and 3 months postoperatively, a 1-sided, McNemar test of non-inferiority of proportions will be performed at an alpha of 0.025 with a delta of 0.10 (10%). This analysis is similar to the approach used for the primary endpoint of cumulative percentage of IOP spikes.

The change in IOP from baseline will be presented by descriptive statistics for the 6-hour, 1-day, 1-week, 1-month and 3-month postoperative time points by OVD group.

Other endpoints, optical/visual symptoms (non-directed) and medical findings/adverse events (non-serious, non-device-related) will be tabulated with frequency and proportion over time and cumulatively by OVD group.

The frequency and proportion of monocular BCDVA will be reported over time by visual acuity line. Monocular BCDVA percent 20/40 or better will also be compared to ISO SPE rate.

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

20.3 GENERAL STATISTICS

Descriptive statistics will typically include sample size (N), mean, standard deviation (SD), minimum (Min) and maximum (Max) as appropriate for continuous variables. For dichotomous variables, the frequency and proportion will be reported and McNemar's test will be applied. For continuous variables, statistical tests (paired t-test) assuming normality will generally be used. For ordinal categorical data, the frequency and proportion will be reported and Wilcoxon signed-rank test will generally be applied.

20.4 INTERIM REPORTS

Due to the short duration of this study, no interim study reports are anticipated. However, should a progress report be required for regulatory purposes (e.g., FDA progress report), all masking will be maintained. If any interim analyses need be performed for product registration or release in other countries that require unmasking and reporting of effectiveness outcomes, they will be conducted by an independent body to avoid bias. Interim reports will not be disseminated to investigators/site personnel or to AMO staff working directly with study sites and monitoring incoming data.

20.5 SAMPLE SIZE CALCULATIONS

Cumulative IOP spikes are defined as an IOP of 30 mm Hg or greater at any visit. The percentage of eyes with IOP spikes will be assumed to be 30% (15798:2001(E), Annex D), and a correlation of 0.5 (medium strength). Using a one-sided, McNemar test and assuming an alpha of 0.025, power = 0.80, and a minimum detectable difference of δ=0.10 yields a sample size of n=195 eyes per group. Adding 20% for lost-to-follow-up and screen failures yields a sample size of up to 241 enrolled subjects with the intent to approximately 230 subjects to ensure 200 evaluable subjects.

Assuming a 1-sided, non-inferiority, paired t-test with alpha=0.025, a common standard deviation of 305 cells[4], and a correlation of 0.50 (medium strength), a sample of n=195 subjects (390 eyes) provides over 99% power to detect a minimum clinically significant decrease in mean Endothelial Cell Count (ECC) of at least δ =125 cells. This corresponds to a 5% decrease using a standard deviation of 12% from a baseline ECC of 2500 cells.

Since the sample size required to detect a minimum clinically significant effect for IOP spikes also provides over 99% power to detect a minimum clinically significant effect for ECC loss, the sample size for the study will be based on the number calculated for IOP spikes. Therefore, the sample size required is 195 subjects. Adding 20% for lost-to-follow-up and screen failures yields a sample size of 241 subjects (482 eyes).

21. REFERENCES

1. Little, R. and Rubin, D. Statistical Analysis with Missing Data, John Wiley & Son, Inc. New York, Second Edition, (2002)

2. Liesegang TJ. Viscoelastic substances in ophthalmology. Surv ophthalmol 1990; 34:268-293

3. Colin J, et al. Comparative clinical trial of AMO Vitrax and Healon use in extracapsular cataract extraction. J Cataract Refract Surg 1995 Mar; 21(2):196-201

4. Nichols JJ, Kosunick M, Bullimore MA. Reliability of Corneal Thickness and Endothelial Cell Density Measures. J Cataract Refract Surg 2003 ;19:344-352

APPENDIX A SUMMARY OF PROCEDURES REQUIRED AT EACH VISIT

Examination	Preop Both Eyes	Op 1 1st Eye	6 hrs 1st Eye	1 day 1st Eye	1 wk 1st Eye	Op 2 2nd Eye	6 hrs 1st Eye	1 day 2nd Eye	1 wk 2nd Eye	1 mo Both Eyes	3 mo Both Eyes
Ocular history, inclusion/exclusion criteria	X										
Informed consent	X										
Potential visual acuity	X										
Randomization		X									
Lens power/serial number/operative procedures		X				X					
UCDVA – photopic, monocular (Snellen)				X				X			
BCDVA - photopic, monocular (Snellen)	X				X				X	X	X
Intraocular pressure (Goldmann)	X		X	X	X		X	X	X	X	X
Endothelial cell count	X										X
Biomicroscopic slit-lamp exam[a]	X		X	X	X		X	X	X	X	X
Dilated fundus exam	X										X[b]
Adverse events		X	X	X	X	X	X	X	X	X	X
Ocular medications	X	X	X	X	X	X	X	X	X	X	X
Ocular/visual symptoms (non-directed)				X	X			X	X	X	X

[a] Includes determination of medical and lens findings/complications
[b] Only if medically indicated

APPENDIX B EQUIPMENT LIST

The following equipment will be supplied to an investigative site for the duration of the study provided that the site does not already have such equipment available for use. This equipment loan will be documented in the Clinical Trial Agreement, which indicates that the equipment is to be returned to Abbott Medical Optics at the completion of the study.

- Konan Specular Microscope (if necessary)
- Aegis Refrigerator and Sensor

APPENDIX C ENDOTHELIAL CELL COUNTS

Endothelial cell counts (ECC) will be performed with a Konan non-contact specular microscope capable of capturing ECC images electronically at both the preoperative and the 3-month visits. Three acceptable images should be taken at each of these two visits. If possible; throughout the study the same technician/photographer at each site should take all the images.

A Konan technician will work directly with each study site to ensure proper calibration of the specular microscope and train/retrain appropriate site staff on the proper technique for capturing quality images. Prior to study initiation, each site must submit two sample images to the central reading center (EyeKor, Inc.) to ensure good quality images with clearly defined endothelial cells.

For preoperative subject qualification, the study technician should record the lowest of the three ECC values on the case report form for each eye. If the lowest value for either eye is below 1800 cells/mm^2, the subject should not be enrolled.

Throughout the course of the study, sites are to send all study images directly to the central reading center for analysis. The preoperative and three-month postoperative images will be sent to EyeKor using EXCELSIOR software without any indication of the treatment group

Analyses will be performed using the mean of the three images for each subject at each time point.

APPENDIX D SLIT-LAMP EXAM RATINGS

A. Ratings of Aqueous Cells and Flare

For consistency across study sites, the SUN (Standardization of Uveitis Nomenclature) Working Group Grading Scheme is to be used for grading of anterior chamber cells and flare as reported in: Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop; The standardization of uveitis nomenclature (SUN) working group, Am J Ophthalmol 2005;140:509-516.

CELLS

Grade	Cells in Field (Field is a 1x1 mm slit beam)
0	<1
0.5+	1 - 5
1+	6 - 15
2+	16 - 25
3+	26 - 50
4+	>50

FLARE

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

B. Ratings of Corneal Edema

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

Amount	Grade	Description
None	**0**	Normal transparency: a. No epithelial or sub-epithelial haziness b. No microcysts c. No stromal cloudiness
Trace	**+1**	a. Barely discernable localized epithelial or sub-epithelial haziness, and/or b. 1 to 20 microcysts, and/or c. Barely discernable localized stromal cloudiness
Mild	**+2**	a. Faint but definite localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness, and/or b. 21-50 microcysts
Moderate	**+3**	a. Significant localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness and/or b. 51-100 microcysts
Severe	**+4**	a. Definite widespread epithelial or stromal cloudiness, giving dull glass appearance to cornea or numerous coalescent bullae (please note the number and location of bullae), and/or b. >100 microcysts or bullae, and/or c. Numerous striae (please note the number and location of striae or folds)

C. Posterior Capsule Striae Grading Scale

The following five-point grading scale is to be used for rating striae in the posterior capsule:

Amount	Grade	Description
None	0	None
Trace	+1	One detectable, barely noticeable striae
Mild	+2	One or two prominent striae
Moderate	+3	Three or more prominent striae, but visibility of retina is not impacted
Severe	+4	Three or more prominent striae affecting visualization of retina

D. Posterior Capsule Opacification Grading Scale

Below is the five-point grading scale to be used for PCO determination:

Amount	Grade	Description
None	0	Normal posterior capsule with no area of opacity. Red reflex bright.
Trace	+1	Some loss of transparency involving the posterior capsule. Red reflex fairly bright
Mild	+2	Mild loss of transparency with cloudiness extending through most of the posterior capsule. There may be a few Elschnig's pearls in the posterior capsule. Red reflex mildly diminished.
Moderate	+3	Moderate loss of transparency with difficulty visualizing the retina. There may be multiple Elschnig's pearls in the posterior capsule. Red reflex markedly diminished.
Severe	+4	Posterior capsule very opaque with inability to view the retina. The posterior capsule may have confluent Elschnig's pearls and fibrous scarring. Red reflex barely visible.

APPENDIX E ADVERSE EVENT AND COMPLAINT REPORTING INSTRUCTIONS

All adverse events and complaints related to using AMO products must be reported to AMO.

ALL ADVERSE EVENTS AND COMPLAINTS:

For events that are not considered serious or related to the study device:

1. Record the event and/or complaint on the case report form that corresponds to the visit during which awareness of the event occurred. Additionally, a complaint may be reported via a telephone call to AMO.
2. Send the completed case report form to AMO in a timely manner

SERIOUS ADVERSE EVENTS OR DEVICE DEFICIENCIES THAT MAY HAVE LED TO A SERIOUS EVENT

In the event of a serious event (i.e., life- or sight-threatening incident) whether or not related to the device, or a device deficiency that may have led to a serious event, the investigator shall:

1. Notify AMO immediately (no more than 48 hours after learning of the event) as follows:
   a. Contact the following AMO personnel by phone and/or email:

      Cheryl Harper
      Mobile: 913-396-3276
      cheryl.harper@abbott.com

      Debbie Trentacost
      Mobile: 714-679-9179
      Office: 714-247-8625
      debbie.trentacost@abbott.com

   b. Submit an SAE/ADE Detailed Page to AMO

NON-SERIOUS, DEVICE-RELATED EVENTS:

For events that are not considered serious but are believed related to the study device (ADEs):

1. Complete an SAE/ADE Detailed Page
2. Ensure the data are submitted to AMO within a timely manner.